

R E M A R K S

This paper is being filed in response to the Office Action dated November 7, 2002 that was issued in connection with the above-identified patent application. Applicants request a one-month extension of time and enclose the fee required pursuant to 37 C.F.R. §1.17(a)(1). Applicants also enclose herewith a Supplemental Information Disclosure Statement, Form PTO-1449, and the fee required pursuant to 37 C.F.R. §§1.17(p) and 1.97(c). Applicants further enclose herewith a Second Substitute Sequence Listing in paper and computer readable form. Applicants respectfully request reconsideration of the instant application in view of the amendments and remarks presented herein.

Claims 39-86 were pending. Claims 52, 57-79, 80-81, and 83-84 have been withdrawn from consideration. Claims 39-41, 52, 54, 57-79, 80-81, and 83-84 have been cancelled herein without prejudice and Claims 42-49, 53, 55-56, 82, and 85-86 have been amended. The amendments are supported by the instant specification and, therefore, do not constitute new matter. Upon entry of the instant Amendment, claims 42-51, 53, 55-56, 82, and 85-86 will be pending.

Rewritten specification paragraphs and claims appear in the preceding "IN THE SPECIFICATION" and "IN THE CLAIMS" sections respectively. Attached hereto is a marked-up version of the changes made by the instant amendment. The attached pages are captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE" and are included pursuant to 37 C.F.R. §1.121(c)(ii). Should any discrepancies be discovered, the version presented in the preceding "IN THE SPECIFICATION" and "IN THE CLAIMS" sections shall take precedence.

Sequence Letter

The Examiner has objected to the specification as containing sequence disclosures, yet allegedly failing to comply with 37 C.F.R. §§1.821-1.825. Applicants traverse this objection and assert that the specification, as amended herein, complies with 37 C.F.R. §§1.821-1.825. Applicants, therefore, respectfully request withdrawal of this objection.

Applicants submit herewith a Second Substitute Sequence Listing in paper and computer readable form. The undersigned hereby states that the content of the paper and computer readable copies of the Second Substitute Sequence Listing submitted in accordance with 37 C.F.R. §1.821(c) and (e), are the same. The undersigned hereby also states that the content of the paper and computer readable copies of the Second Substitute Sequence Listing, submitted in accordance with 37 C.F.R. §1.821(g), herein does not include new matter.

Applicants Second Substitute Sequence Listing corrects typographical errors in the sequences presented in the original application. Applicants enclose herewith five sequence alignments (Alignments 1-5) for the Examiner's review wherein corrections are highlighted. In each case, the Examiner's attention is respectfully invited to the  sequences which provide support for the changes.

Drawings

The Examiner has objected to the drawings on the grounds that the Brief Description of the Drawings allegedly fails to refer to multiple frames. Applicants assert that the Brief Description of the Drawings, as amended herein, fully complies with MPEP §608.01(f) and, therefore, respectfully request withdrawal of this objection.

Claims Are Drawn to Statutory Subject Matter

The Examiner has rejected claims 39-43, 45-47, and 55-56 under 35 U.S.C. §101 as allegedly reading on a product of nature. Applicants traverse this rejection and assert that the claims are drawn to statutory subject matter. Applicants assert that it is unnecessary to recite "isolated" or "purified" in the instant claims because a polypeptide having the amino acid sequence of SEQ ID NO:8 and nucleic acids which encode such a polypeptide do not occur in nature. *See e.g.* Example 8 and Figures 4A and 4B. Since the engineered molecules having the sequences of SEQ ID NOS:7 and 8 respectively display the requisite "hand of man and do not otherwise occur in nature, Applicants respectfully request withdrawal of this rejection.

The Examiner has also rejected claims 43 and 48-51 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph as allegedly unsupported by a specific and substantial asserted utility or a well established utility.

Applicants traverse this rejection and assert that the claims, as amended herein, are drawn to statutory subject matter having specific, substantial, and credible utility. The risks and consequences of human exposure to botulinum neurotoxin are readily apparent to those of ordinary skill in the art and, indeed, to society at large. Applicants assert that the nucleic acids, the polypeptides, and the methods of the invention have use, *inter alia*, in immunization of humans and mammals against botulinum neurotoxin toxicity. *See e.g.* Example 10, page 41, lines 8-24 and Table 6. Therefore, Applicants respectfully request withdrawal of these rejections.

Claims Are Supported by Sufficient Description

Claims 39-42, 43, 44-51, 55-56, 82, and 85-86 have been rejected under 35 U.S.C. §112, first paragraph as allegedly lacking sufficient description to convey to one skilled in the art that Applicants were in possession of the invention at the time of filing. The Examiner alleges that the description does not support the breadth of claims drawn to a genus of nucleic acids where only one species is provided and the claim(s) do not recite a specific function of the nucleic acids.

Applicants traverse this rejection and assert that the claims, as amended herein, are fully supported by the description such that one of ordinary skill in the art would readily appreciate that Applicants were in possession of the invention on or before the filing date. Claims 39-41 have been cancelled rendering rejection of these claims moot. Claim 43 has been amended to independent form. Support for this amendment may be found in the specification as filed at, *inter alia*, Examlpe 8 and Figure 4. Therefore, Applicants respectfully request withdrawal of this rejection.

Claims Are Enabled by the Description

Claim 54 has been rejected under 35 U.S.C. §112, first paragraph as drawn to subject matter that allegedly is not described in the specification in such a way as to enable one skilled in the art to make and use the invention. The Examiner has alleged that the recombinant organism of claim 54 does not produce, express, or comprise a coding sequence for botulinum neurotoxin.

Claim 54 has been cancelled. Applicant's response to this rejection is directed to claim 53. Applicants traverse this rejection and assert that claim 53, as amended herein, is fully enabled by the specification as filed. The transfected cell of claim 53 comprises "an expression vector comprising a nucleic acid having a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:8." Moreover, the method of claim 53 comprises culturing this organism "under conditions wherein the nucleic acid is expressed". This claim has ample support in the specification at, *inter alia*, Examples 3 and 8. Therefore, Applicants respectfully request withdrawal of this rejection.

Claims Are Clear and Definite

Claims 39-51, 53-56, 82, 85, and 86 have been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly reciting non-elected inventions. Applicants assert that the claims, as amended herein, do not recited non-elected subject matter.

Claims 39-41 have been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for use of the phrases "encodes the carboxy-terminal portion" (claim 39), "is capable of" (claim 39), "the gram negative bacteria is Escherichia coli" (claim 40), and "the yeast is Pichia pastoris". Applicants respectfully submit that these rejections are moot since claims 39-41 have been cancelled.

Claim 43 has been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly reciting neither a function nor a specific structure. Applicants traverse this rejection and assert that claim 43, as amended herein, recites both a structure and a function. Applicants assert further that this claim is broader than the original claim in that it recites SEQ ID NO:8 rather than SEQ ID NO:7.

Claim 44 has been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the phrase "wherein the nucleic acid is a synthetic nucleic acid". Claim 44, as amended herein, does not recite this phrase.

Claims 45 and 46 have been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly lacking antecedent basis for the recited expression control sequence. Applicants have amended claim 45 to recite "further comprising" according to the Examiner's suggestion.

Claim 48 has been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the word "organism" in reference to mammalian cell lines. Claim 48 has been amended herein to replace the word "organism" with the word "cell".

Claim 48 has also been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the phrase "transfected an organism with the nucleic acid of claim 39". The Examiner has alleged that the nucleic acid of claim 39 is defined as any portion of the carboxy-terminus of botulinum neurotoxin heavy chain and therefore, is not required to encode a botulinum neurotoxin. The Examiner has requested clarification as to what is encoded by the nucleic acid and what is expressed therefrom.

Applicants traverse this rejection and assert that claim 48, as amended herein, clearly sets forth what is encoded by the nucleic acid and what is expressed therefrom. Applicants respectfully invite the Examiner's attention to the phrase "a nucleic acid having a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:8" in relation to what is encoded by the nucleic acid. In addition, Applicants respectfully invite the Examiner's attention to the phrase "comprising at least one immunogenic epitope" in relation to what is expressed. Applicants assert that one of ordinary skill in the art would recognize that

while all or substantially all of the nucleic acid may be expressed by the recombinant cell of claim 48, the polypeptide comprising a carboxy-terminal portion of the heavy chain of botulinum neurotoxin serotype B comprising at least one immunogenic epitope constitutes less than the full-length of SEQ ID NO:8. In view of these and other amendments, Applicants assert that claim 48 is clear and definite.

Claim 49 has been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly lacking antecedent basis for the term "protein". The Examiner has alleged that it is unclear whether the carboxy-terminal is a part of the "protein". The Examiner has also alleged that it is unclear what "protein" is being recovered. Applicants traverse this rejection and assert that claim 49, as amended herein, satisfies the requirements of 35 U.S.C. §112, second paragraph.

Claim 53 has been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly failing to recite method steps that correspond with the preamble. The Examiner has alleged that claim 53 fails to recite expression or isolation of a heavy chain portion or preparation or formulation of an immunogenic composition. Claim 53 has also bee rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the phrase "in expressible form".

Applicants traverse this rejection and assert that claim 53, as amended herein, claims the subject method in a manner that complies with 35 U.S.C. §112, second paragraph. Applicants respectfully invite the Examiner's attention to the phrase "recovering from said transfected cell at least one insoluble polypeptide" recited by amended claim 53. In view of this phrase and other amendments, Applicants assert that the method steps of amended claim 53 correspond to the preamble. In addition, amended claim 53 does not recite the phrase "in expressible form".

Claim 54 has been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the phrase "recovering an insoluble protein fraction". This rejection will be moot upon entry of the instant Amendment whereby claim 54 has been cancelled.

Claims 85 and 86 have been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly lacking antecedent basis for the term "protein". Claims 85 and 86 have been amended to recite "polypeptide" as is clearly recited in amended claim 43.

For the foregoing reasons, Applicants believe that the claims comply with the requirements of 35 U.S.C. §112, second paragraph and, therefore, respectfully request withdrawal of these rejections.

Claims Are Novel over the Cited Documents

Claims 43, 48, and 53 are independent claims. Claims 42, 44-47, 55-56, 82, and 85-86 depend from claim 43. Claims 49-51 depend from claim 48. For a reference to anticipate, it must teach each and every element of the subject claim. *See e.g.* MPEP §2131. Since a dependent claim is to be construed to include all of the limitations of the claim from which it depends, *see e.g.* 37 C.F.R. §1.75(c), a document that fails to teach an element of an independent claim necessarily fails to teach an element of an attendant dependent claim. Therefore, Applicants will respond to the following rejections primarily as they apply to claims 43, 48, and 53.

1. Campbell Does Not Teach SEQ ID NO:8

Claims 39-47, 54-56, and 82-86 have been rejected under 35 U.S.C. §102(a) as allegedly unpatentable over Campbell KD et al., 1993, *J. Clin. Microbiol.* 31(9):2255-2262 (hereinafter "Campbell"). The Examiner has alleged that Campbell teaches a nucleic acid

sequence of the carboxy-terminal of a botulinum neurotoxin of SEQ ID NO:7 and encodes a portion of SEQ ID NO:8.

Applicants traverse this rejection and assert that the claims, as amended herein, are not anticipated by Campbell. This rejection will be moot as to claims 39-41 and 54 upon entry of the instant Amendment in view of the cancellation of these claims herein. Applicants note that the Examiner has included non-elected claims 83 and 84 in this rejection. Applicants suspect that this is a simple clerical error, but respectfully request clarification.

Claims 43, 48, and 53 each recite a "a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope". Applicants respectfully invite the Examiner's attention to Alignments 6-9 attached hereto, which show that Eklund 2B and NCTC 7273 of Campbell are not the same as SEQ ID NOS:7 an 8 of the present invention. Therefore, since Eklund 2B and NCTC 7273 of Campbell fail to teach SEQ ID NO:8 herein, Campbell fails to anticipate each and every element of claims 43, 48, and 53. Consequently, Applicants respectfully request withdrawal of this rejection.

2. Smith 1998 Does Not Teach SEQ ID NO:8

Claims 39, 41, 48, and 51 have been rejected under 35 U.S.C. §102(a) as allegedly unpatentable over Smith LA, 1998, *Toxicon* 36(11):1539-1548 (hereinafter "Smith 1998"). The Examiner has alleged that Smith 1998 discloses a nucleic acid encoding a Clostridium botulinum type B heavy chain capable of being expressed in *Pichia pastoris*. The Examiner has further alleged that Smith 1998 discloses a method of producing an immunogenic composition comprising culturing a recombinant *Pichia pastoris* cell and recovering the expressed heavy chain polypeptide.

Applicants traverse this rejection and assert that Smith 1998 does not anticipate the claimed invention. This rejection will be moot as to claims 39 and 41 upon entry of the instant Amendment in view of the cancellation of these claims herein. Claim 48, as amended herein, recites “transfected a cell with a nucleic acid having a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope”. Smith 1998 does not teach the amino acid sequence of SEQ ID NO:8. Since Smith 1998 does not teach each and every element of the claimed invention, Applicants respectfully request withdrawal of this rejection.

3. Halpern Does Not Teach SEQ ID NO:8

Claims 39-47, 54-56, and 82-86 have been rejected under 35 U.S.C. §102(a) as allegedly unpatentable over Halpern JL et al., 1993, *J. Biol. Chem.* 268(15):11188-11192 (hereinafter “Halpern”). The Examiner has alleged that Halpern discloses a nucleic acid that has a nucleotide sequence encoding the carboxy-terminal portion of a botulinum neurotoxin, wherein the nucleic acid encodes an amino acid sequence that is conserved across Clostridial neurotoxins including serotype B. The Examiner has further alleged that Halpern discloses a nucleic acid encoding the amino acid sequence Asp-Glu-Gly-Trp-Thr. In addition, Halpern allegedly discloses antibody and immunogenic composition preparation and nucleic acid expression with a T7 RNA polymerase promoter. It also has been alleged that Halpern discloses expression of the nucleic acids of Halpern in recombinant mammalian host cells as well as recovery of the expressed protein.

Applicants traverse this rejection and assert that the claims, as amended herein, are not anticipated by Halpern. This rejection will be moot as to claims 39-41 and 54 upon entry of the instant Amendment in view of the cancellation of these claims herein. Applicants note

that the Examiner has included non-elected claims 83 and 84 in this rejection. Applicants suspect that this is a simple clerical error, but respectfully request clarification.

Claims 43 and 53 each recite a "a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope". Applicants respectfully invite the Examiner's attention to Alignment 10 attached hereto which shows that the sequence of Halpern is not the same as the polypeptide sequence of SEQ ID NO:8 of the present invention. Therefore, since Halpern fails to teach Smith SEQ ID NO:8, Halpern fails anticipate each and every element of claims 43 and 53. Consequently, Applicants respectfully request withdrawal of this rejection.

4. Whalen Does Not Teach SEQ ID NO:8

Claims 39-47, 53-56, 82, and 85-86 have been rejected under 35 U.S.C. §102(b) as allegedly unpatentable over Whelan SM et al., April 26, 1993, Accession M81186 GI:144743 (hereinafter "Whalen"). Whalen allegedly discloses a nucleic acid which encodes the carboxy-terminal portion of the heavy chain of botulinum neurotoxin serotype B. The Examiner has alleged that the nucleic acid of Whalen would be capable of expression in an organism selected from the group consisting of gram negative bacteria, yeast, and a mammalian cell line.

Applicants traverse this rejection and assert that the claims, as amended herein, are not anticipated by Whalen. As a preliminary matter, Applicants request clarification of two issues related to this rejection. First, Applicants note that the Office Action dated November 7, 2002 indicated that Accession M81186 was published on May 28, 1992. Applicants respectfully invite the Examiner's attention to an enclosed printout of the Sequence Revision History that Applicants obtained from <http://www.ncbi.nlm.nih.gov/entrez/sutils/girevhist.cgi>, which indicates that the nucleotide and amino acid sequences assigned Accession M81186 were "first

seen at NCBI on Apr 26 1993 16:35". Therefore, Applicants respectfully request clarification of the basis for the Examiner's use of the May 28, 1992 date.

Second, the Examiner has stated "[t]he nucleic acid was cloned and found to encode a polypeptide of 623 amino acids of the H chain (see abstract)". Paper 11, Office Action dated November 11, 2002, p. 17, paragraph 23, lines 7-8. However, Applicants respectfully invite the Examiner's attention to the disclosure published by NCBI as Accession M81186 and note that there is no abstract and very little annotation of any kind. Moreover, the annotation that is present discloses an amino acid sequence of 1291 amino acids, not 623 amino acids. Applicants, therefore, respectfully request clarification.

This rejection will be moot as to claims 39-41 and 54 upon entry of the instant Amendment in view of the cancellation of these claims herein.

Claims 43 and 53 each recite a "a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope". Applicants respectfully invite the Examiner's attention to Alignments 11 and 12 attached hereto, which show that the sequence of Accession No. M81186 is not the same as the sequences of SEQ ID NOS:7 and 8 respectively of the present invention. Therefore, since Whalen fails to teach the instant SEQ ID NO:8, Whalen fails anticipate each and every element of claims 43 and 53. Applicants further contend that the nucleic acid of Whalen, with total AT content of 74.56% and an AT content over the aligned region of 76.45%, would be nonexpressible in yeast and poorly expressible or nonexpressible in gram negative bacteria and mammalian cell lines. *See e.g.* page 14, lines 20-22. Consequently, Applicants respectfully request withdrawal of this rejection.

5. Jung Does Not Teach SEQ ID NO:8

Claims 39-50, 53-56, 82, and 85-86 have been rejected under 35 U.S.C. §102(b) as allegedly unpatentable over Jung HH et al., 1992, *FEMS Microbiol Lett.* **91**:69-72 (hereinafter "Jung"). Jung allegedly discloses a nucleotide sequence that encodes a carboxy-terminal portion of the heavy chain of a botulinum neurotoxin serotype B. The Examiner alleges that the nucleic acid of Jung comprises a nucleotide sequence selected from SEQ ID NO:7 and would encode an amino acid sequence of SEQ ID NO:8.

Applicants traverse this rejection and assert that Jung fails to anticipate the instant invention. This rejection will be moot as to claims 39-41 and 54 upon entry of the instant Amendment in view of the cancellation of these claims herein.

Applicants respectfully invite the Examiner's attention to the title and the Summary of Jung, both of which clearly indicate that Jung relates to the **amino**-terminal end of the heavy chain of botulinum neurotoxin serotype B. Applicants claims relate to the **carboxy**-terminal end of the heavy chain of botulinum neurotoxin serotype B. Applicants further invite the Examiner's attention to Alignments 13 and 14 attached hereto, which show that Jung is not the same as SEQ ID NOS:7 and 8. Therefore, Jung clearly fails to teach a nucleic acid of Smith SEQ ID NO:7 that encodes an amino acid sequence of Smith SEQ ID NO:8.

Moreover, contrary to the Examiner's assertion that the sequence of Jung would naturally evidence an AT content of less than 60%-70%, the nucleic acid of Jung actually has an AT content of 75.87% over the region for which the nucleotide sequence is disclosed. Moreover, one of ordinary skill in the art would **not** expect the full-length sequence to deviate from this figure substantially, since it is well known to those of skill in the art that the native neurotoxin genes of *Clostridium botulinum* are known to have a **high** AT content. *See e.g.* page 14, lines 7-

11 and Whalen (full-length AT = 74.56%). Therefore, Jung neither expressly teaches nor inherently discloses SEQ ID NO:8 or a sequence which encodes it. Consequently, Applicants respectfully request withdrawal of this rejection.

6. The '665 Patent Does Not Teach SEQ ID NO:8

Claims 39-47 and 55-56 have been rejected under 35 U.S.C. §102(e) as allegedly unpatentable over U.S. Patent No. 5,919,665 to Williams et al. (hereinafter "the '665 patent"). The Examiner has alleged that a portion of SEQ ID NO:7 is 100% identical to a portion of SEQ ID NO:22, 25 or 27 of the '665 patent.

Applicants traverse this rejection and assert that the claims, as amended herein, are not anticipated by the '665 patent. This rejection will be moot as to claims 39-41 and 54 upon entry of the instant Amendment in view of the cancellation of these claims herein.

Claims 43, 48, and 53 each recite a "a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope". Applicants respectfully invite the Examiner's attention to Alignments 15-20 attached hereto, which show that SEQ ID NOS:22, 25, and 27 of the '665 patent and the respective polypeptides encoded thereby, *i.e.* SEQ ID NOS:23, 26, and 28, are not the same as invention SEQ ID NOS:7 and 8 of the present invention. Therefore, since SEQ ID NOS: 22, 23, and 25-28 of the '665 patent fail to teach SEQ ID NO:8 of the present invention, the '665 patent fails anticipate each and every element of claims 43, 48, and 53. Consequently, Applicants respectfully request withdrawal of this rejection of these independent claims as well as the attendant dependent claims.

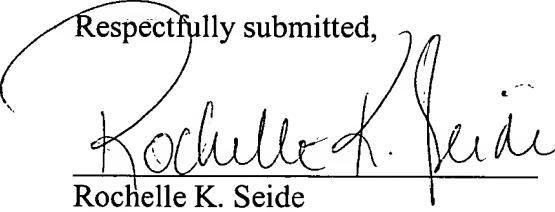
In conclusion, claims 42-51, 53, 55-56, 82, and 85-86 are drawn to statutory subject matter, recite language that complies with 35 U.S.C. §112, and are not anticipated by any

of the asserted documents. Therefore, Applicants believe this application is in condition for allowance and respectfully request issuance of a Notice of Allowance.

Applicants note that the Office Action dated November 7, 2002 included several sequence alignments. However, Applicants found it difficult to interpret these alignments due to the absence of meaningful labels and/or the poor quality of the photocopies provided. Therefore, should the Examiner continue to maintain any of the foregoing art rejections, Applicants respectfully request new alignments with clear labels identifying which invention sequence is aligned with which sequence of the asserted art.

Applicants request a one-month extension of time and enclose the fee required pursuant to 37 C.F.R. §1.17(a)(1). Applicants also enclose the fee required pursuant to 37 C.F.R. §1.17(p) and 1.97(c). Applicants do not believe that any additional fees are due with this submission. Nevertheless, the Commissioner is hereby authorized to charge any fees due with this submission not otherwise enclosed herewith to Deposit Account No. 02-4377. Please credit any overpayment of fees associated with this filing to the above-identified deposit account. A duplicate of this page is enclosed. A copy of the Notice to Comply is also enclosed.

Respectfully submitted,


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Enclosures

VERSION WITH MARKINGS TO SHOW CHANGES MADE

This marked-up version was prepared with DeltaView software (v2.7). In this section, added text is marked with double underlining. *e.g.* added text, and deleted text is marked by a single strikethrough, *e.g.* ~~deleted text~~.

IN THE SPECIFICATION

The paragraphs beginning at page 6, line 20 and ending at page 6, line 32 have been **amended** as follows:

~~It is an object of this~~The instant invention to provideprovides immunogenic peptides capable of eliciting protective immunity against botulinum neurotoxin of serotypes A-G.

~~It is another object of this~~The instant invention toalso provideprovides vaccines capable of eliciting protective immunity against botulinum neurotoxin, where the vaccines do not act as neurotoxins themselves.

~~It is yet another object of this~~The instant invention tofurther provideprovides methods for preparing non-toxic peptides for use in vaccines against botulinum neurotoxin by growing recombinant organisms which express the peptides.

~~It is still another object of this~~The instant invention ~~to also provide~~provides methods for fast and efficient purification of the non-toxic peptides from cultures of recombinant organisms.

These and other ~~objects~~aspects are ~~met~~illustrated by one or more of the following embodiments of the present invention.

The paragraphs beginning at page 9, line 20 and ending at page 11, line 12 have been **amended** as follows:

~~Figure 1 shows the~~Figures 1A and 1B respectively show the nucleotide sequence and the encoded amino acid sequence for a synthetic gene encoding the H_c fragment of BoNT serotype A (SEQ ID NOS:1 and the encoded amino acids sequence2).

~~Figure 2 shows the~~Figures 2A and 2B respectively show the nucleotide sequence and the encoded amino acid sequence for a synthetic gene encoding the H_c fragment of BoNT serotype A (SEQ ID NOS:3 and the encoded amino acids sequence4).

~~Figure 3 shows the Figures 3A and 3B respectively~~
~~show the nucleotide sequence and the encoded amino acid~~
~~sequence for a synthetic gene encoding the H_c fragment of~~
~~BoNT serotype A (SEQ ID NOS:5 and the encoded amino acids~~
~~sequence6).~~

~~Figure 4 shows the Figures 4A and 4B respectively~~
~~show the nucleotide sequence and the encoded amino acid~~
~~sequence for a synthetic gene encoding the H_c fragment of~~
~~BoNT serotype B (SEQ ID NOS:7 and the encoded amino acids~~
~~sequence8).~~

~~Figure 5 shows the Figures 5A and 5B respectively~~
~~show the nucleotide sequence and the encoded amino acid~~
~~sequence for a synthetic gene encoding the H_c fragment of~~
~~BoNT serotype C (SEQ ID NOS:9 and the encoded amino acids~~
~~sequence10).~~

~~Figure 6 shows the Figures 6A and 6B respectively~~
~~show the nucleotide sequence and the encoded amino acid~~
~~sequence for a synthetic gene encoding the H_c fragment of~~
~~BoNT serotype D (SEQ ID NOS:11 and the encoded amino acids~~
~~sequence12).~~

~~Figure 7 shows the Figures 7A and 7B respectively~~
~~show the nucleotide sequence and the encoded amino acid~~

sequence for a synthetic gene encoding the H_c fragment of BoNT serotype E (SEQ ID NOS:13) and the encoded amino acids sequence14).

Figure 8 shows the nucleotide sequence for a synthetic gene encoding the H_c fragment of BoNT serotype E and the encoded amino acidsacid sequence (SEQ ID NOS:35 and 36).

~~Figure 9 shows the~~Figures 9A and 9B respectively show the nucleotide sequence and the encoded amino acid sequence for a synthetic gene encoding the H_c fragment of BoNT serotype F (SEQ ID NOS:15) and the encoded amino acids sequence16).

~~Figure 10 shows the~~Figures 10A and 10B respectively show the nucleotide sequence and the encoded amino acid sequence for a synthetic gene encoding the H_c fragment of BoNT serotype G (SEQ ID NOS:17) and the encoded amino acids sequence18).

~~Figure 11 shows the~~Figures 11A and 11B respectively show the nucleotide sequence and the encoded amino acid sequence for a synthetic gene encoding the H_N fragment of BoNT serotype A (SEQ ID NOS:19) and the encoded amino acids sequence20).

Figure 12 shows the Figures 12A and 12B
respectively show the nucleotide sequence and the encoded
amino acid sequence for a synthetic gene encoding the H_N
fragment of BoNT serotype B (SEQ ID NOS:21 and the encoded
amino acids sequence22).

Figure 13 shows the Figures 13A and 13B
respectively show the nucleotide sequence and the encoded
amino acid sequence for a synthetic gene encoding the H_N
fragment of BoNT serotype C (SEQ ID NOS:23 and the encoded
amino acids sequence24).

Figure 14 shows the Figures 14A and 14B
respectively show the nucleotide sequence and the encoded
amino acid sequence for a synthetic gene encoding the H_N
fragment of BoNT serotype D (SEQ ID NOS:25 and the encoded
amino acids sequence26).

Figure 15 shows the Figures 15A and 15B
respectively show the nucleotide sequence and the encoded
amino acid sequence for a synthetic gene encoding the H_N
fragment of BoNT serotype E (SEQ ID NOS:27 and the encoded
amino acids sequence28).

Figure 16 shows the Figures 16A and 16B
respectively show the nucleotide sequence and the encoded

amino acid sequence for a synthetic gene encoding the H_N fragment of BoNT serotype F (SEQ ID NOS:29 and the encoded amino acids sequence30).

Figure 17 shows the Figures 17A and 17B respectively show the nucleotide sequence and the encoded amino acid sequence for a synthetic gene encoding the H_N fragment of BoNT serotype G (SEQ ID NOS:31 and the encoded amino acids sequence32).

Figure 18 shows the Figures 18A and 18B respectively show the nucleotide sequence and the encoded amino acid sequence for a synthetic gene encoding the H_C fragment of BoNT serotype F (SEQ ID NOS:33 and the encoded amino acids sequence34).

Figures 19A, 19B, and 19C. Figure 19A shows (A) the AT base content of a putative fragment C region in native *C. botulinum* DNA. (Figure 19B) Reduction at shows the reduced AT content after the first design (rBoNTF(Hc)1) of the synthetic gene. (Figure 19C) shows the AT content of the final gene design (rBoNTF(Hc)2) used to express recombinant rBoNTF(Hc) in *P. pastoris*.

Figures 20A and 20B. Figure 20A shows (A) an SDS-PAGE gel and (Figure 20B) shows a Western blot of samples

at various steps along the rBoNTF(Hc) purification. Lanes from both figures are identical except lane 1, where SDS-PAGE shows Novex mark 12 wide-range molecular weight markers and Western blot shows Novex See Blue prestained molecular weight markers. Lane 2 is the cell lysate, lane 3 is the cell extract, lane 4 is the cell extract after dialysis, lane 5 is pool of rBoNTF(Hc) positive fractions after Mono S column chromatography, and lane 6 is pool of rBoNTF(Hc)-positive fractions after hydrophobic interaction chromatography.

FigureFigures 21—showsA and 21B show purification of rBoNTF(Hc) by sequential chromatography. {Figure 21A} shows Mono S cation exchange chromatography of extract from *P. pastoris*. Proteins were eluted with increasing NaCl gradient. Fractions positive for rBoNTF(Hc) by Western analysis were pooled individually and subjected to hydrophobic interaction chromatography (the results of which are shown in Figure 21B) and proteins were eluted with a decreasing ammonium sulfate gradient. In both panels, protein monitored by A280nm is recorded on the left axis and elution conditions are recorded on the right axis, with the gradient trace laid over the chromatogram.

The paragraph beginning at page 12, line 7 and ending at page 12, line 14 has been **amended** as follows:

Kozaki et al. (in "Antibodies against Botulism Neurotoxin", L.L. Simpson, ed., 1989, Academic Press, New York) suggested that a protective epitope might be present in the 50 kDa carboxyl terminus (HC) region of the protein. Thompson et al. (1990, *Eur. J. Biochem.* **189**:73-81) deduced the amino acid sequence for the serotype A botulinum toxin. DasGupta, et al. (1990, *Biochemie*, **72**:661-664) identified the "nick" site for post-translational cleavage of the expressed toxin polypeptide, from which the sequence of the heavy chain can be deduced as follows (see SEQ ID NO:41. See also Kriegstein, et al., 1994, *J. Protein Chem.*, **13**:49-57):

The paragraph beginning at page 13, line 1 and ending at page 13, line 6 has been **amended** as follows:

Whelan et al. (*Appl. Environ. Microbiol.* **58**:2345-2354, 1992) have deduced the amino acid sequence for the serotype B botulinum toxin. Schmidt, et al. (1985, *Arch. Biochem. Biophys.*, **238**:544-548) provided N-terminal sequence information for the heavy chain resulting from

post-translational cleavage of the expressed toxin polypeptide, and the sequence of the heavy chain can be deduced from this information as follows SEQ ID NO:42.

The paragraph beginning at page 36, line 17 and ending at page 36, line 17 has been **amended** as follows:

The sequence of the C fragment of the A chain was deduced as SEQ ID NO:38.

The paragraph beginning at page 36, line 32 and ending at page 36, line 32 has been **amended** as follows:

The sequence for the synthetic gene is found below SEQ ID NO:37.

The paragraph beginning at page 38, line 6 and ending at page 38, line 7 has been **amended** as follows:

The C fragment for botulism toxin serotype B of Whelan was studied and the portion of the protein having the sequence of SEQ ID NO:40 was defined as the C fragment.

The paragraph beginning at page 38, line 18 and ending at page 38, line 25 has been **amended** as follows:

The synthetic gene for expression in *E. coli* was produced in the manner described for synthesis of the gene for the C fragment of the A strand, namely, using a large number of oligomers of approximately 60-65 bases corresponding to the sequences of the + and - strands with overlaps of 7 bases. The oligomers were allowed to anneal and were ligated to form subunits of 250-300 base pairs each. Each subunit had been designed to have restriction sites at their termini which allowed them to be assembled in the right order to form the complete gene. ~~the~~The synthetic gene ~~for~~ encoding the eC fragment of the B toxin ~~was as follows~~is SEQ ID NO:39.

IN THE CLAIMS

Claims 42-49, 53, 55, 82, and 85-86 have been **amended** as follows:

42. (AMENDED) The nucleic acid of claim 39,43, wherein
said nucleic acid ~~comprises a nucleic acid~~nucleotide
sequence ~~selected from the group consisting of~~is SEQ
ID No. 7, SEQ ID No. 9, SEQ ID No. 11, SEQ ID No. 13,
SEQ ID No. 15, and SEQ ID No. 17.NO:7.

43. (AMENDED) A nucleic acid ~~comprising~~having a
nucleotide sequence which ~~encodes~~encoding a
polypeptide ~~having~~ an comprising the amino acid
sequence ~~selected from the group consisting of~~of SEQ ID
No. NO:8, SEQ ID No. ~~said amino acid sequence comprising~~
at least one immunogenic epitope. 10, SEQ ID No. 12,
SEQ ID No. 14, SEQ ID No. 16, and SEQ ID No. 18.

44. (AMENDED) The nucleic acid of claim 39,43, wherein
said nucleic acid is ~~a~~an ~~synthetic~~isolated nucleic
acid.

45. (AMENDED) The nucleic acid of claim 39, ~~wherein said~~
~~nucleic acid is operably linked to~~43 further
comprising an expression control sequence~~sequence~~sequence
operably linked to said nucleotide sequence.

46. (AMENDED) The nucleic acid of claim 39,45, wherein
said expression control sequenceessequence
~~comprise~~comprises a promoter.

47. (AMENDED) The nucleic acid of claim 39,45, wherein
said expression control sequenceessequence
~~comprise~~comprises an enhancer.

48. (AMENDED) A method of preparing a polypeptide
comprising ~~the~~a carboxy-terminal portion of the heavy
chain of a-botulinum neurotoxin ~~serotype selected from~~
~~the group consisting of~~ serotype B comprising at least
one immunogenic epitope, ~~serotype C₁~~, ~~serotype D~~,
~~serotype E~~, ~~serotype F~~, and ~~serotype G~~, said method
comprising:

transfecting ~~an organism~~a cell with ~~the~~a nucleic
acid having a nucleotide sequence encoding a
polypeptide having the amino acid sequence of
claim 39, SEQ ID NO:8, said amino acid sequence
comprising at least one immunogenic epitope; and

culturing the transfected ~~organism~~cell under
conditions wherein the ~~carboxy terminal portion~~
~~of the heavy chain of a botulinum neurotoxin~~
~~serotype~~nucleic acid is expressed,

wherein the organismcell is selected from the group consisting of a gram negative bacteria, a yeast, and a mammalian cell line.

49. (AMENDED) The method of claim 48, further comprising recovering insoluble protein from said transfected organismcell at least one insoluble polypeptide having the amino acid sequence of SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope.

53. (AMENDED) A method of preparing thean immunogenic composition comprising a polypeptide comprising the amino acid sequence of claim 52, SEQ ID NO:8, said method amino acid sequence comprising at least one immunogenic epitope, comprising :

culturing a recombinant host organismcell transfected with an expression vector comprising a nucleic acid comprising a nucleotide sequence encoding, in an expressable form, a polypeptide comprising the carboxy terminal portion amino acid sequence of SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope under conditions wherein the heavy chain of a botulinum

neurotoxin serotype nucleic acid is expressed;

and

recovering from said transfected cell at least one
insoluble polypeptide comprising the amino acid
sequence of SEQ ID NO:8, said amino acid sequence
comprising at least one immunogenic epitope,

wherein the cell is selected from the group consisting
of a gram negative bacteria, a yeast, and a mammalian
cell.

55. (AMENDED) The nucleic acid of claim 39,43, wherein the A+TAT content is less than about 70% of the total base composition.
56. (AMENDED) The nucleic acid of claim 55, wherein the A+TAT content is less than about 60% of the total base composition.
82. (TWICE AMENDED) A recombinant host cell comprising the nucleic acid of claim 39.45.
85. (AMENDED) The recombinant host cell of claim 82, wherein said proteinpolypeptide is at least 0.75% (w/w) of the total cellular protein.

86. (AMENDED) The recombinant host cell of claim 85,
wherein said proteinpolypeptide is at least 20% (w/w)
of the total cellular protein.

IN THE SEQUENCE LISTING

The following alignments show the changes made to the indicated sequences and the support for these changes based on other sequences in the application. In this section, a summary of changes appears just before each alignment and changes are highlighted in the alignments. (SI# = SEQ ID NO; Ac# M81186 = Genbank accession number M81186, a copy of which is attached.)

Alignment 1

SEQ ID NO:41 (appearing on page 12 in the specification as filed) has been amended as follows:

- At position 717 of paragraph 1.8, Y has been inserted.
- At position 822 of paragraph 1.10, O→Q.

Paragraph 1.1

	1	15	16	30	31	45	46	60	61	75	76	90
As filed	ALNDLCIKVNNWDLF	FSPSEDNFTNDLNKG	EEITSDTNIEAAEEN	ISLDLIQQYLTNFN	DNEPENISIENLSSD	IIGQLELMPNIERFP						90
Amended	ALNDLCIKVNNWDLF	FSPSEDNFTNDLNKG	EEITSDTNIEAAEEN	ISLDLIQQYLTNFN	DNEPENISIENLSSD	IIGQLELMPNIERFP						90
P.36 SI#38	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig.3 SI#6	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig.2 SI#4	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig.1 SI#2	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0

Paragraph 1.2

	91	105	106	120	121	135	136	150	151	165	166	180
As filed	NGKKYELDKYTMFHY	LRAQEFEHGKSRIAL	TNSVNEALLNPSRVY	TFSSDYVKKVNKAT	EAAMFLGWVEQLVYD	FTDETSEVSTTDKIA						180
Amended	NGKKYELDKYTMFHY	LRAQEFEHGKSRIAL	TNSVNEALLNPSRVY	TFSSDYVKKVNKAT	EAAMFLGWVEQLVYD	FTDETSEVSTTDKIA						180
P.36 SI#38	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig.3 SI#6	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig.2 SI#4	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig.1 SI#2	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0

Paragraph 1.3

	181	195	196	210	211	225	226	240	241	255	256	270
As filed	DITIIIPYIGPALNI	GMLYKDDFVGALIFS	GAVILLEFIPEIAIP	VLGTFALVSYIANKV	LTVQTIDNALSKRNE	KWDEVYKYIVTNWLA						270
Amended	DITIIIPYIGPALNI	GMLYKDDFVGALIFS	GAVILLEFIPEIAIP	VLGTFALVSYIANKV	LTVQTIDNALSKRNE	KWDEVYKYIVTNWLA						270
P.36 SI#38	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig.3 SI#6	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig.2 SI#4	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig.1 SI#2	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0

Paragraph 1.4

	271	285	286	300	301	315	316	330	331	345	346	360
As filed	KVNTQIDLIRKKMKE	ALENQAEATKAINY	QYNQYTEEKNNINF	NIDDLSSKLNESINK	AMININKFLNQCSV	YLMNSMIPYGVKLE						360
Amended	KVNTQIDLIRKKMKE	ALENQAEATKAINY	QYNQYTEEKNNINF	NIDDLSSKLNESINK	AMININKFLNQCSV	YLMNSMIPYGVKLE						360
P.36 SI#38	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig.3 SI#6	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig.2 SI#4	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig.1 SI#2	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0

Paragraph 1.5

361	375	376	390	391	405	406	420	421	435	436	450
As filed	DFDASLKDALLKYIR	DNYGTLIGQVDRLLKD	KVNNTLSTDIPFQLS	KYVDNQRLLSTFTEY	IKNIINTSILNLRYE	SNHLIDLSRYASKIN					450
Amended	DFDASLKDALLKYIR	DNYGTLIGQVDRLLKD	KVNNTLSTDIPFQLS	KYVDNQRLLSTFTEY	IKNIINTSILNLRYE	SNHLIDLSRYASKIN					450
P.36 SI#38	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	18
Fig.3 SI#6	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	38
Fig.2 SI#4	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	37
Fig.1 SI#2	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	40

Paragraph 1.6

451	465	466	480	481	495	496	510	511	525	526	540
As filed	IGSKVNFDPIDKNQI	QLFNLESSKIEVILK	NAIVNSMYENFSTS	FWIRIPKYFNISLN	NEYTIINCENNNSGW	KVSLNYGEIIWTLQD					540
Amended	IGSKVNFDPIDKNQI	QLFNLESSKIEVILK	NAIVNSMYENFSTS	FWIRIPKYFNISLN	NEYTIINCENNNSGW	KVSLNYGEIIWTLQD					540
P.36 SI#38	IGSKVNFDPIDKNQI	QLFNLESSKIEVILK	NAIVNSMYENFSTS	FWIRIPKYFNISLN	NEYTIINCENNNSGW	KVSLNYGEIIWTLQD					108
Fig.3 SI#6	IGSKVNFDPIDKNQI	QLFNLESSKIEVILK	NAIVNSMYENFSTS	FWIRIPKYFNISLN	NEYTIINCENNNSGW	KVSLNYGEIIWTLQD					128
Fig.2 SI#4	IGSKVNFDPIDKNQI	QLFNLESSKIEVILK	NAIVNSMYENFSTS	FWIRIPKYFNISLN	NEYTIINCENNNSGW	KVSLNYGEIIWTLQD					127
Fig.1 SI#2	IGSKVNFDPIDKNQI	QLFNLESSKIEVILK	NAIVNSMYENFSTS	FWIRIPKYFNISLN	NEYTIINCENNNSGW	KVSLNYGEIIWTLQD					130

Paragraph 1.7

541	555	556	570	571	585	586	600	601	615	616	630
As filed	TQEIKQRVVFQYSQM	INISDYINRWFVTI	TNNRLNNNSKIYTING	RLIDQKPISNLGNIH	ASNNIMFKLDGCRDT	HRYIWIKYFNLFDKE					630
Amended	TQEIKQRVVFQYSQM	INISDYINRWFVTI	TNNRLNNNSKIYTING	RLIDQKPISNLGNIH	ASNNIMFKLDGCRDT	HRYIWIKYFNLFDKE					630
P.36 SI#38	TQEIKQRVVFQYSQM	INISDYINRWFVTI	TNNRLNNNSKIYIN-G	RLIDQKPISNLGNIH	ASNNIMFKLDGCRDT	HRYIWIKYFNLFDKE					197
Fig.3 SI#6	TQEIKQRVVFQYSQM	INISDYINRWFVTI	TNNRLNNNSKIYIN-G	RLIDQKPISNLGNIH	ASNNIMFKLDGCRDT	HRYIWIKYFNLFDKE					217
Fig.2 SI#4	TQEIKQRVVFQYSQM	INISDYINRWFVTI	TNNRLNNNSKIYIN-G	RLIDQKPISNLGNIH	ASNNIMFKLDGCRDT	HRYIWIKYFNLFDKE					216
Fig.1 SI#2	TQEIKQRVVFQYSQM	INISDYINRWFVTI	TNNRLNNNSKIYIN-G	RLIDQKPISNLGNIH	ASNNIMFKLDGCRDT	HRYIWIKYFNLFDKE					219

Paragraph 1.8

631	645	646	660	661	675	676	690	691	705	706	720
As filed	LNEKEIKDLYDNQSN	SGILKDFWGDLQYD	KPYYMILLYDPNKV	DVNNVGIRGYMLKG	PRGSVMTTNIYLNS	LYRGTKFIKK-ASG					719
Amended	LNEKEIKDLYDNQSN	SGILKDFWGDLQYD	KPYYMILLYDPNKV	DVNNVGIRGYMLKG	PRGSVMTTNIYLNS	LYRGTKFIKKYASG					719
P.36 SI#38	LNEKEIKDLYDNQSN	SGILKDFWGDLQYD	KPYYMILLYDPNKV	DVNNVGIRGYMLKG	PRGSVMTTNIYLNS	LYRGTKFIKKYASG					287
Fig.3 SI#6	LNEKEIKDLYDNQSN	SGILKDFWGDLQYD	KPYYMILLYDPNKV	DVNNVGIRGYMLKG	PRGSVMTTNIYLNS	LYRGTKFIKKYASG					307
Fig.2 SI#4	LNEKEIKDLYDNQSN	SGILKDFWGDLQYD	KPYYMILLYDPNKV	DVNNVGIRGYMLKG	PRGSVMTTNIYLNS	LYRGTKFIKKYASG					306
Fig.1 SI#2	LNEKEIKDLYDNQSN	SGILKDFWGDLQYD	KPYYMILLYDPNKV	DVNNVGIRGYMLKG	PRGSVMTTNIYLNS	LYRGTKFIKKYASG					309

Paragraph 1.9

721	735	736	750	751	765	766	780	781	795	796	810
As filed	NKDNIVRNNDRVYIN	VVVKNKEYRLATNAS	QAGVEKILSALEIPD	VGNLSQVVMKSKND	QGITNKCKMNLQDNN	GNDIGFIGFHOFNNI					809
Amended	NKDNIVRNNDRVYIN	VVVKNKEYRLATNAS	QAGVEKILSALEIPD	VGNLSQVVMKSKND	QGITNKCKMNLQDNN	GNDIGFIGFHOFNNI					809
P.36 SI#38	NKDNIVRNNDRVYIN	VVVKNKEYRLATNAS	QAGVEKILSALEIPD	VGNLSQVVMKSKND	QGITNKCKMNLQDNN	GNDIGFIGFHOFNNI					377
Fig.3 SI#6	NKDNIVRNNDRVYIN	VVVKNKEYRLATNAS	QAGVEKILSALEIPD	VGNLSQVVMKSKND	QGITNKCKMNLQDNN	GNDIGFIGFHOFNNI					397
Fig.2 SI#4	NKDNIVRNNDRVYIN	VVVKNKEYRLATNAS	QAGVEKILSALEIPD	VGNLSQVVMKSKND	QGITNKCKMNLQDNN	GNDIGFIGFHOFNNI					396
Fig.1 SI#2	NKDNIVRNNDRVYIN	VVVKNKEYRLATNAS	QAGVEKILSALEIPD	VGNLSQVVMKSKND	QGITNKCKMNLQDNN	GNDIGFIGFHOFNNI					399

Paragraph 1.10

811	825	826	840	841	855	856	870	871	885	886	900
As filed	AKLVASNWYRTER	SSRTLGCSEWEFIPVD	DGWGERPL	846							
Amended	AKLVASNWYRQTER	SSRTLGCSEWEFIPVD	DGWGERPL	847							
P.36 SI#38	AKLVASNWYRQIER	SSRTLGCSEWEFIPVD	DGWGERPL	415							
Fig.3 SI#6	AKLVASNWYRQIER	SSRTLGCSEWEFIPVD	DGWGERPL	435							
Fig.2 SI#4	AKLVASNWYRQIER	SSRTLGCSEWEFIPVD	DGWGERPL	434							
Fig.1 SI#2	AKLVASNWYRQIER	SSRTLGCSEWEFIPVD	DGWGERPL	437							

Alignment 2

SEQ ID NO:42 (appearing on page 13 in the specification as filed) has been amended as follows:

- At position 911 of paragraph 2.11, T→V.
- At position 969 of paragraph 2.11, N has been inserted.
- At position 1110 of paragraph 2.13, T has been deleted.
- At position 1193 of paragraph 2.14, K has been inserted.
- At position 1254 of paragraph 2.14, V→Y.
- At position 1257 of paragraph 2.14, V→Y.
- At position 1262 of paragraph 2.15, D→K.
- At position 1269 of paragraph 2.15, K has been inserted.

Paragraph 2.1

	1	15 16	30 31	45 46	60 61	75 76	90	
As filed	-	-	-	-	-	-	-	0
Amended	-	-	-	-	-	-	-	0

Fig 4 SI#8

Ac#	M81186	MPVTINNFNYNDPID	NNNIIMMEPPFARGT	GRYYKAFKITDRIWI	IPERYTFGYKPEDFN	KSSGIFNRDVCEYYD	PDYLNTNDKKNIFLQ	90
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Paragraph 2.2

	91	105 106	120 121	135 136	150 151	165 166	180	
As filed	-	-	-	-	-	-	-	0
Amended	-	-	-	-	-	-	-	0

Fig 4 SI#8

Ac#	M81186	TMIKLFNRIKSPLG	EKLLEMIINGIPYLG	DRRVPLEEFNTNIAS	VTVNKLISNPGEVER	KKGIFANLIIFGPGP	VLNENETIDIGIQNH	180
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Paragraph 2.3

	181	195 196	210 211	225 226	240 241	255 256	270	
As filed	-	-	-	-	-	-	-	0
Amended	-	-	-	-	-	-	-	0

Fig 4 SI#8

Ac#	M81186	FASREGFGGIMQMKF	CPEYVSVFNNQENK	GASIFNRRGYFSDPA	LILMHELIHLHGLY	GIKVDDLPIVPNEKK	FFMQSTDAIQAEELY	270
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Paragraph 2.4

	271	285 286	300 301	315 316	330 331	345 346	360	
As filed	-	-	-	-	-	-	-	0
Amended	-	-	-	-	-	-	-	0

Fig 4 SI#8

Ac#	M81186	TFGGQDPSIITPSTD	KSIYDKVLQNFRGIV	DRLNKVLVCISDPNI	NINIYKNFKDKYKF	VEDSEGKYSIDVESF	DKLYKSLMFGFTETN	360
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Paragraph 2.5

	361	375 376	390 391	405 406	420 421	435 436	450	
As filed	-	-	-	-	-	-	-	APGICIDVD 9
Amended	-	-	-	-	-	-	-	APGICIDVD 9

Fig 4 SI#8

Ac#	M81186	IAENYKIKTRASYFS	DSLPPVKIKNLLDNE	IYTIEEGFNISDKDM	EKEYRGQNKAINQQA	YEEISKEHLAVYKIQ	MCKSVKAPGICIDVD	450
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Paragraph 2.6

451	465	466	480	481	495	496	510	511	525	526	540
As filed	NEDLFFIADKNSFSD	DLSKNERIEYNTQSN	YIENDFPINELILD	T	DLISKIELPSENTE	LTD	FNV	DVPVY	EKQP	AIKKIFTDENTIFQY	99
Amended	NEDLFFIADKNSFSD	DLSKNERIEYNTQSN	YIENDFPINELILD	T	DLISKIELPSENTE	LTD	FNV	DVPVY	EKQP	AIKKIFTDENTIFQY	99

Fig 4 SI#8

Ac# M81186 NEDLFFIADKNSFSD DLSKNERIEYNTQSN YIENDFPINELILD DLISKIELPSENTE LTD FNV DVPVY EKQP AIKKIFTDENTIFQY 540

Paragraph 2.7

541	555	556	570	571	585	586	600	601	615	616	630
As filed	LYSQTFPLDIRDISL	TSSFDALLFSNKVY	SFFSM	YIKTANKVV	EAGLFAGWVKQIVND	FVIEANKSNTMDKIA	DISLIVPYIGLALNV				189
Amended	LYSQTFPLDIRDISL	TSSFDALLFSNKVY	SFFSM	YIKTANKVV	EAGLFAGWVKQIVND	FVIEANKSNTMDKIA	DISLIVPYIGLALNV				189

Fig 4 SI#8

Ac# M81186 LYSQTFPLDIRDISL TSSFDALLFSNKVY SFFSM YIKTANKVV EAGLFAGWVKQIVND FVIEANKSNTMDKIA DISLIVPYIGLALNV 630

Paragraph 2.8

631	645	646	660	661	675	676	690	691	705	706	720
As filed	GNETAKGNFENAFEI	AGASILLEFIPPELLI	PVVGAF	LLESYIDNK	NKIIK	TIDNALT	KRN	EKWS	SDMYGLIV	AQWL	STVN
Amended	GNETAKGNFENAFEI	AGASILLEFIPPELLI	PVVGAF	LLESYIDNK	NKIIK	TIDNALT	KRN	EKWS	SDMYGLIV	AQWL	STVN

Fig 4 SI#8

Ac# M81186 GNETAKGNFENAFEI AGASILLEFIPPELLI PVVGAF LLESYIDNK NKIIK TIDNALT KRN EKWS SDMYGLIV AQWL STVN QFYTKEGMY 720

Paragraph 2.9

721	735	736	750	751	765	766	780	781	795	796	810
As filed	KALNYQAQALEEEIIK	YRYNIYSEKEKSNN	IDFD	NDINSKLN	NEG	QAI	DNINNF	INGCSV	SYLM	KKMIPL	AVEKL
Amended	KALNYQAQALEEEIIK	YRYNIYSEKEKSNN	IDFD	NDINSKLN	NEG	QAI	DNINNF	INGCSV	SYLM	KKMIPL	AVEKL

Fig 4 SI#8

Ac# M81186 KALNYQAQALEEEIIK YRYNIYSEKEKSNN IDFD NDINSKLN NEG QAI DNINNF INGCSV SYLM KKMIPL AVEKL LDFDNTLKKNLLNYI 810

Paragraph 2.10

811	825	826	840	841	855	856	870	871	885	886	900
As filed	DENKLYLIGSAEYEK	SKVN	KYLKT	IMPFDL	SIYT	NTD	ILIE	MFNK	YNE	SEIL	LN
Amended	DENKLYLIGSAEYEK	SKVN	KYLKT	IMPFDL	SIYT	NTD	ILIE	MFNK	YNE	SEIL	LN

Fig 4 SI#8

Ac# M81186 DENKLYLIGSAEYEK SKVN

Paragraph 2.11

901	915	916	930	931	945	946	960	961	975	976	990
As filed	LTSSANSKIRVTQ	NQ	NIIFNSV	FLDFSV	WIRIP	KYKNDG	QNY	IHN	EYTI	INC	MKNNS
Amended	LTSSANSKIRVTQ	NQ	NIIFNSV	FLDFSV	WIRIP	KYKNDG	QNY	IHN	EYTI	INC	MKNNS

Fig 4 SI#8

Ac# M81186 LTSSANSKIRVTQ NQ NIIFNSV FLDFSV WIRIP KYKNDG QNY IHN EYTI INC MKNNS GWKISIRGNRIIWTL IDINGKTKSVFFEYN 990

Paragraph 2.12

991	1005	1006	1020	1021	1035	1036	1050	1051	1065	1066	1080
As filed	IREDISEYINRWF	FF	TIT	NNL	NN	NAK	YING	KLES	NTD	DIK	DIRE
Amended	IREDISEYINRWF	FF	TIT	NNL	NN	NAK	YING	KLES	NTD	DIK	DIRE

Fig 4 SI#8

Ac# M81186 IREDISEYINRWF FF TIT NNL NNL NAK YING KLES NTD DIK DIRE ANGEIIFKLDGDIDR TQFIW MKYFSIFNTE LSQS

Paragraph 2.13

1081	1095	1096	1110	1111	1125	1126	1140	1141	1155	1156	1170
As filed	SEYLKDFWGNPLMYN	KEYYMFNAGNKN	SYT	IKL	KKD	SPV	GEIL	TR	SKY	QN	SKY
Amended	SEYLKDFWGNPLMYN	KEYYMFNAGNKN	SYT	IKL	KKD	SPV	GEIL	TR	SKY	QN	SKY

Fig 4 SI#8

Ac# M81186 SEYLKDFWGNPLMYN KEYYMFNAGNKN SYT IKL KKD SPV GEIL TR SKY QN SKY INYRDL YIGEKFII RRSNSQ SINDDIVRKEDYIYL 1169

Paragraph 2.14

1171	1185	1186	1200	1201	1215	1216	1230	1231	1245	1246	1260
As filed	DFFN	LNQ	EW	RV	Y	Y	Y	Y	Y	Y	Y
Amended	DFFN	LNQ	EW	RV	Y	Y	Y	Y	Y	Y	Y

Fig 4 SI#8

Ac# M81186 DFFN LNQ EW RV Y Y Y Y Y Y Y Y Y Y Y Y ESTDEIGLIGIHRFY ESGIVFEEVKDVFCI 1259

Paragraph 2.15

1261	1275	1276	1290	1291	1305	1306	1320	1321	1335	1336	1350
As filed	SDWY	LEVK	R	KPYNL	KLGC	NWQ	FIP	KD	GW	TE	848
Amended	SKWY	LEVK	R	KPYNL	KLGC	NWQ	FIP	KD	GW	TE	850

Fig 4 SI#8

Ac# M81186 SKWY LEVK R KPYNL KLGC NWQ FIP KD GW TE 1291 440 1291

Alignment 3

SEQ ID NO:37 (appearing on page 37 in the specification as filed) has been amended as follows:

- At position 147 of paragraph 3.2, C→G.
- At position 287 of paragraph 3.4, G is inserted.
- At position 535 of paragraph 3.6, G is inserted.
- At position 583 of paragraph 3.7, C is inserted.
- At position 956 of paragraph 3.11, D→C.
- At positions 957-959 of paragraph 3.11, GTT is inserted.

*No. identical metric
also significant*

Paragraph 3.1											
1	15	16	30	31	45	46	60	61	75	76	90
As filed	---	CTCGAGCCATGG	CTCGTCTGCTGCTA	CCTTCAGTGAATACA	TCAAGAACATCATCA	ATACCTCCATCCTGA	ACCTGCGCTACGAAT				87
Amended	---	CTCGAGCCATGG	CTCGTCTGCTGCTA	CCTTCAGTGAATACA	TCAAGAACATCATCA	ATACCTCCATCCTGA	ACCTGCGCTACGAAT				87
Fig.1	SI#1	GAATTCGAAACGATG	CGT--CTGCTGCTA	CCTTCAGTGAATACA	TCAAGAACATCATCA	ATACCTCCATCCTGA	ACCTGCGCTACGAAT				88
Fig.3	SI#5	GAATTCGAAACGATG	G-----CCTCTA	CCTTCAGTGAATACA	TCAAGAACATCATCA	ATACCTCCATCCTGA	ACCTGCGCTACGAAT				82
Fig.2	SI#3	GAATTCGAAACGATG	T-----CTA	CCTTCAGTGAATACA	TCAAGAACATCATCA	ATACCTCCATCCTGA	ACCTGCGCTACGAAT				79

Paragraph 3.2											
91	105	106	120	121	135	136	150	151	165	166	180
As filed	CCAATCACCTGATCG	ACCTGTCCTCGCTACG	CTTCCAAAATCAACA	TCGGTTCTAAACTTA	ACTTCGATCCGATCG	ACAAGAACATCAGATCC					177
Amended	CCAATCACCTGATCG	ACCTGTCCTCGCTACG	CTTCCAAAATCAACA	TCGGTTCTAAAGTTA	ACTTCGATCCGATCG	ACAAGAACATCAGATCC					177
Fig.1	SI#1	CCAATCACCTGATCG	ACCTGTCCTCGCTACG	CTTCCAAAATCAACA	TCGGTTCTAAAGTTA	ACTTCGATCCGATCG	ACAAGAACATCAGATCC				178
Fig.3	SI#5	CCAATCACCTGATCG	ACCTGTCCTCGCTACG	CTTCCAAAATCAACA	TCGGTTCTAAAGTTA	ACTTCGATCCGATCG	ACAAGAACATCAGATCC				172
Fig.2	SI#3	CCAATCACCTGATCG	ACCTGTCCTCGCTACG	CTTCCAAAATCAACA	TCGGTTCTAAAGTTA	ACTTCGATCCGATCG	ACAAGAACATCAGATCC				169

Paragraph 3.3											
181	195	196	210	211	225	226	240	241	255	256	270
As filed	AGCTGTTCAATCTGG	AACTTCCAAAATCG	AAAGTTACCTCTGAAGA	ATGCTATCGTATACA	ACTCTATGTACGAAA	ACTTCTCCACCTCCT					267
Amended	AGCTGTTCAATCTGG	AACTTCCAAAATCG	AAAGTTACCTCTGAAGA	ATGCTATCGTATACA	ACTCTATGTACGAAA	ACTTCTCCACCTCCT					267
Fig.1	SI#1	AGCTGTTCAATCTGG	AACTTCCAAAATCG	AAAGTTACCTCTGAAGA	ATGCTATCGTATACA	ACTCTATGTACGAAA	ACTTCTCCACCTCCT				268
Fig.3	SI#5	AGCTGTTCAATCTGG	AACTTCCAAAATCG	AAAGTTACCTCTGAAGA	ATGCTATCGTATACA	ACTCTATGTACGAAA	ACTTCTCCACCTCCT				262
Fig.2	SI#3	AGCTGTTCAATCTGG	AACTTCCAAAATCG	AAAGTTACCTCTGAAGA	ATGCTATCGTATACA	ACTCTATGTACGAAA	ACTTCTCCACCTCCT				259

Paragraph 3.4											
271	285	286	300	301	315	316	330	331	345	346	360
As filed	TCTGGATCCGTATCC	C-AAATACCTCAACT	CCATCTCTCTGAACA	ATGAATACACCATCA	TCAACTCGATGGAAA	ACAATTCTGGTTGGA					356
Amended	TCTGGATCCGTATCC	CGAAATACCTCAACT	CCATCTCTCTGAACA	ATGAATACACCATCA	TCAACTCGATGGAAA	ACAATTCTGGTTGGA					357
Fig.1	SI#1	TCTGGATCCGTATCC	CGAAATACCTCAACT	CCATCTCTCTGAACA	ATGAATACACCATCA	TCAACTCGATGGAAA	ACAATTCTGGTTGGA				358
Fig.3	SI#5	TCTGGATCCGTATCC	CGAAATACCTCAACT	CCATCTCTCTGAACA	ATGAATACACCATCA	TCAACTCGATGGAAA	ACAATTCTGGTTGGA				352
Fig.2	SI#3	TCTGGATCCGTATCC	CGAAATACCTCAACT	CCATCTCTCTGAACA	ATGAATACACCATCA	TCAACTCGATGGAAA	ACAATTCTGGTTGGA				349

Paragraph 3.5											
361	375	376	390	391	405	406	420	421	435	436	450
As filed	AAGTATCTCTGAACT	ACGGTGAAATCATCT	GGACTCTGCAGGACA	CTCAGGAAATCAAAC	AGCGTGTGTATTCA	AATACTCTCAGATGA					446
Amended	AAGTATCTCTGAACT	ACGGTGAAATCATCT	GGACTCTGCAGGACA	CTCAGGAAATCAAAC	AGCGTGTGTATTCA	AATACTCTCAGATGA					447
Fig.1	SI#1	AAGTATCTCTGAACT	ACGGTGAAATCATCT	GGACTCTGCAGGACA	CTCAGGAAATCAAAC	AGCGTGTGTATTCA	AATACTCTCAGATGA				448
Fig.3	SI#5	AAGTATCTCTGAACT	ACGGTGAAATCATCT	GGACTCTGCAGGACA	CTCAGGAAATCAAAC	AGCGTGTGTATTCA	AATACTCTCAGATGA				442
Fig.2	SI#3	AAGTATCTCTGAACT	ACGGTGAAATCATCT	GGACTCTGCAGGACA	CTCAGGAAATCAAAC	AGCGTGTGTATTCA	AATACTCTCAGATGA				439

Paragraph 3.6

451	465	466	480	481	495	496	510	511	525	526	540	535
As filed	TCACATCTCTGACT	ACATCAATCGCTGGA	TCTTCGTTACCATCA	CCAACAATCGCTG	ATAACTCCAAATCT	ACATCAACG-CCGTC						537
Amended	TCACATCTCTGACT	ACATCAATCGCTGGA	TCTTCGTTACCATCA	CCAACAATCGCTG	ATAACTCCAAATCT	ACATCAACGCCCGTC						538
Fig.1 SI#1	TCACATCTCTGACT	ACATCAATCGCTGGA	TCTTCGTTACCATCA	CCAACAATCGCTG	ATAACTCCAAATCT	ACATCAACGCCCGTC						532
Fig.3 SI#5	TCACATCTCTGACT	ACATCAATCGCTGGA	TCTTCGTTACCATCA	CCAACAATCGCTG	ATAACTCCAAATCT	ACATCAACGCCCGTC						529
Fig.2 SI#3	TCACATCTCTGACT	ACATCAATCGCTGGA	TCTTCGTTACCATCA	CCAACAATCGCTG	ATAACTCCAAATCT	ACATCAACGCCCGTC						529

Paragraph 3.7

541	555	556	570	571	585	586	600	601	615	616	630	624
As filed	TGATCGACCAGAAC	CGATCTCAATCTGG	GTAAACATCCACG-TT	CTAATAACATCATGT	TCAAACGGACGGTT	GTCGTGACACTCACC						627
Amended	TGATCGACCAGAAC	CGATCTCAATCTGG	GTAAACATCCACGCTT	CTAATAACATCATGT	TCAAACGGACGGTT	GTCGTGACACTCACC						628
Fig.1 SI#1	TGATCGACCAGAAC	CGATCTCAATCTGG	GTAAACATCCACGCTT	CTAATAACATCATGT	TCAAACGGACGGTT	GTCGTGACACTCACC						622
Fig.3 SI#5	TGATCGACCAGAAC	CGATCTCAATCTGG	GTAAACATCCACGCTT	CTAATAACATCATGT	TCAAACGGACGGTT	GTCGTGACACTCACC						619
Fig.2 SI#3	TGATCGACCAGAAC	CGATCTCAATCTGG	GTAAACATCCACGCTT	CTAATAACATCATGT	TCAAACGGACGGTT	GTCGTGACACTCACC						619

Paragraph 3.8

631	645	646	660	661	675	676	690	691	705	706	720	714
As filed	GCTACATCTGGATCA	AATACTTCATCTGT	TGACACAAAGAACTGA	ACGAAAAAGAAATCA	AAGACCTGTACGAC	ACCAGTCCAATTCTG						717
Amended	GCTACATCTGGATCA	AATACTTCATCTGT	TGACACAAAGAACTGA	ACGAAAAAGAAATCA	AAGACCTGTACGAC	ACCAGTCCAATTCTG						718
Fig.1 SI#1	GCTACATCTGGATCA	AATACTTCATCTGT	TGACACAAAGAACTGA	ACGAAAAAGAAATCA	AAGACCTGTACGAC	ACCAGTCCAATTCTG						712
Fig.3 SI#5	GCTACATCTGGATCA	AATACTTCATCTGT	TGACACAAAGAACTGA	ACGAAAAAGAAATCA	AAGACCTGTACGAC	ACCAGTCCAATTCTG						709
Fig.2 SI#3	GCTACATCTGGATCA	AATACTTCATCTGT	TGACACAAAGAACTGA	ACGAAAAAGAAATCA	AAGACCTGTACGAC	ACCAGTCCAATTCTG						709

Paragraph 3.9

721	735	736	750	751	765	766	780	781	795	796	810	804
As filed	GTATCCTGAAAGACT	TCTGGGGTGA	TACCTAC	TGCACTACGACAAAC	CGTACTACATGCTG	ATCTGTA	CGATCGCGA	ACAAATACGTTGACG				807
Amended	GTATCCTGAAAGACT	TCTGGGGTGA	TACCTAC	TGCACTACGACAAAC	CGTACTACATGCTG	ATCTGTA	CGATCGCGA	ACAAATACGTTGACG				808
Fig.1 SI#1	GTATCCTGAAAGACT	TCTGGGGTGA	TACCTAC	TGCACTACGACAAAC	CGTACTACATGCTG	ATCTGTA	CGATCGCGA	ACAAATACGTTGACG				802
Fig.3 SI#5	GTATCCTGAAAGACT	TCTGGGGTGA	TACCTAC	TGCACTACGACAAAC	CGTACTACATGCTG	ATCTGTA	CGATCGCGA	ACAAATACGTTGACG				799
Fig.2 SI#3	GTATCCTGAAAGACT	TCTGGGGTGA	TACCTAC	TGCACTACGACAAAC	CGTACTACATGCTG	ATCTGTA	CGATCGCGA	ACAAATACGTTGACG				809

Paragraph 3.10

811	825	826	840	841	855	856	870	871	885	886	900	894
As filed	TCAACAAATGTA	TCCGCGGTTACATGT	ACCTGAAAGGTCCGC	GTGTTCTGTATGA	CTACCAACATCTACC	TGAAC	CTTCCCTGT					897
Amended	TCAACAAATGTA	TCCGCGGTTACATGT	ACCTGAAAGGTCCGC	GTGTTCTGTATGA	CTACCAACATCTACC	TGAAC	CTTCCCTGT					898
Fig.1 SI#1	TCAACAAATGTA	TCCGCGGTTACATGT	ACCTGAAAGGTCCGC	GTGTTCTGTATGA	CTACCAACATCTACC	TGAAC	CTTCCCTGT					892
Fig.3 SI#5	TCAACAAATGTA	TCCGCGGTTACATGT	ACCTGAAAGGTCCGC	GTGTTCTGTATGA	CTACCAACATCTACC	TGAAC	CTTCCCTGT					889
Fig.2 SI#3	TCAACAAATGTA	TCCGCGGTTACATGT	ACCTGAAAGGTCCGC	GTGTTCTGTATGA	CTACCAACATCTACC	TGAAC	CTTCCCTGT					889

Paragraph 3.11

901	915	916	930	931	945	946	960	961	975	976	990	981
As filed	ACCGTGGTACCAAT	TCATCATCAAGAAAT	ACCGCTCTGGTA	ACGACAATATD---C	GCAACAAATGATCGT	TATACATCAATGTTG						987
Amended	ACCGTGGTACCAAT	TCATCATCAAGAAAT	ACCGCTCTGGTA	ACGACAATATGCTTC	GCAACAAATGATCGT	TATACATCAATGTTG						988
Fig.1 SI#1	ACCGTGGTACCAAT	TCATCATCAAGAAAT	ACCGCTCTGGTA	ACGACAATATGCTTC	GCAACAAATGATCGT	TATACATCAATGTTG						982
Fig.3 SI#5	ACCGTGGTACCAAT	TCATCATCAAGAAAT	ACCGCTCTGGTA	ACGACAATATGCTTC	GCAACAAATGATCGT	TATACATCAATGTTG						979
Fig.2 SI#3	ACCGTGGTACCAAT	TCATCATCAAGAAAT	ACCGCTCTGGTA	ACGACAATATGCTTC	GCAACAAATGATCGT	TATACATCAATGTTG						979

Paragraph 3.12

991	1005	1006	1020	1021	1035	1036	1050	1051	1065	1066	1080	1071
As filed	TAGTTAAGAACAAAG	AATACCGTCTGGCTA	CCAATGCTTCTCAGG	CTGGTGTAGAAAAGA	TCTTGCTGCTGCTG	AAATCCCGGACGTTG						1077
Amended	TAGTTAAGAACAAAG	AATACCGTCTGGCTA	CCAATGCTTCTCAGG	CTGGTGTAGAAAAGA	TCTTGCTGCTGCTG	AAATCCCGGACGTTG						1078
Fig.1 SI#1	TAGTTAAGAACAAAG	AATACCGTCTGGCTA	CCAATGCTTCTCAGG	CTGGTGTAGAAAAGA	TCTTGCTGCTGCTG	AAATCCCGGACGTTG						1072
Fig.3 SI#5	TAGTTAAGAACAAAG	AATACCGTCTGGCTA	CCAATGCTTCTCAGG	CTGGTGTAGAAAAGA	TCTTGCTGCTGCTG	AAATCCCGGACGTTG						1069
Fig.2 SI#3	TAGTTAAGAACAAAG	AATACCGTCTGGCTA	CCAATGCTTCTCAGG	CTGGTGTAGAAAAGA	TCTTGCTGCTGCTG	AAATCCCGGACGTTG						1069

Paragraph 3.13

1081	1095	1096	1110	1111	1125	1126	1140	1141	1155	1156	1170	1161
As filed	GTAATCTGCTCAGG	TAGTTGTAATGAAT	CCAAGAACGACCA	GTAATCA	ACAAATGAATCTG	AGGACAACAAATGGTA						1167
Amended	GTAATCTGCTCAGG	TAGTTGTAATGAAT	CCAAGAACGACCA	GTAATCA	ACAAATGAATCTG	AGGACAACAAATGGTA						1168
Fig.1 SI#1	GTAATCTGCTCAGG	TAGTTGTAATGAAT	CCAAGAACGACCA	GTAATCA	ACAAATGAATCTG	AGGACAACAAATGGTA						1162
Fig.3 SI#5	GTAATCTGCTCAGG	TAGTTGTAATGAAT	CCAAGAACGACCA	GTAATCA	ACAAATGAATCTG	AGGACAACAAATGGTA						1159
Fig.2 SI#3	GTAATCTGCTCAGG	TAGTTGTAATGAAT	CCAAGAACGACCA	GTAATCA	ACAAATGAATCTG	AGGACAACAAATGGTA						1159

Paragraph 3.14

1171	1185	1186	1200	1201	1215	1216	1230	1231	1245	1246	1260	1251
As filed	ACGATATCGGTTCA	TCGGTTCCACCA	TCAACAAATATCGCTA	AACTGGTTGCTTCA	ACTGGTACAATCGTC	AGATCGAACGTTCC						1257
Amended	ACGATATCGGTTCA	TCGGTTCCACCA	TCAACAAATATCGCTA	AACTGGTTGCTTCA	ACTGGTACAATCGTC	AGATCGAACGTTCC						1258
Fig.1 SI#1	ACGATATCGGTTCA	TCGGTTCCACCA	TCAACAAATATCGCTA	AACTGGTTGCTTCA	ACTGGTACAATCGTC	AGATCGAACGTTCC						1252
Fig.3 SI#5	ACGATATCGGTTCA	TCGGTTCCACCA	TCAACAAATATCGCTA	AACTGGTTGCTTCA	ACTGGTACAATCGTC	AGATCGAACGTTCC						1249
Fig.2 SI#3	ACGATATCGGTTCA	TCGGTTCCACCA	TCAACAAATATCGCTA	AACTGGTTGCTTCA	ACTGGTACAATCGTC	AGATCGAACGTTCC						1249

Paragraph 3.15

	1261	1275	1276	1290	1291	1305	1306	1320	1321	1335	1336	1350
As filed	CTCGCACTCTGGGTT	GCTCTTGGGAGTTCA		TCCCGGTTGATGACG		GTTGGGGTGAACGTC	CGCTGTAACCCGGGA	AAGCTT				1332
Amended	CTCGCACTCTGGGTT	GCTCTTGGGAGTTCA		TCCCGGTTGATGACG		GTTGGGGTGAACGTC	CGCTGTAACCCGGGA	AAGCTT				1338
Fig.1 SI#1	CTCGCACTCTGGGTT	GCTCTTGGGAGTTCA		TCCCGGTTGATGACG		GTTGGGGTGAACGTC	CGCTGTAAGAATTTC-	-----				1332
Fig.3 SI#5	CTCGCACTCTGGGTT	GCTCTTGGGAGTTCA		TCCCGGTTGATGACG		GTTGGGGTGAACGTC	CGCTGTAAGAATTTC-	-----				1326
Fig.2 SI#3	CTCGCACTCTGGGTT	GCTCTTGGGAGTTCA		TCCCGGTTGATGACG		GTTGGGGTGAACGTC	CGCTGTAAGAATTTC-	-----				1323

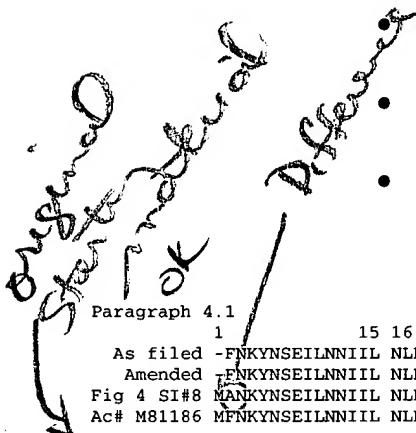
Alignment 4

SEQ ID NO:40 (appearing on page 38 in the specification as filed) has been amended as follows:

At position 121 of paragraph 4.2, T→I.

At position 327 of paragraph 4.4, Q→W.

At position 334 of paragraph 4.4, K→Y.



As filed	-FNKYNSEILNNIIL	NLRYKDNNLIDL	SGY	GAKVEVYDGVELNDK	NQFKLTSSANSKIRV	TQNQNIIFNSVFLDF	SVSFWIRIPKYKNDG	89
Amended	FNKYNSEILNNIIL	NLRYKDNNLIDL	SGY	GAKVEVYDGVELNDK	NQFKLTSSANSKIRV	TQNQNIIFNSVFLDF	SVSFWIRIPKYKNDG	89
Fig 4 SI#8	MANKYNSEILNNIIL	NLRYKDNNLIDL	SGY	GAKVEVYDGVELNDK	NQFKLTSSANSKIRV	TQNQNIIFNSVFLDF	SVSFWIRIPKYKNDG	90
Ac# M81186	MFNKNSEILNNIIL	NLRYKDNNLIDL	SGY	GAKVEVYDGVELNDK	NQFKLTSSANSKIRV	TQNQNIIFNSVFLDF	SVSFWIRIPKYKNDG	90

Paragraph 4.2	1	15 16	30 31	45 46	60 61	75 76	90
As filed	IQNYIHNEYTIINCM	KNNSGWKISIRGNRI	TWTLIDINGKTKS	FEYNIREDISEYINR	WFFVTITNNLNNAKI	YINGKLESNTDIKDI	179
Amended	IQNYIHNEYTIINCM	KNNSGWKISIRGNRI	TWTLIDINGKTKS	FEYNIREDISEYINR	WFFVTITNNLNNAKI	YINGKLESNTDIKDI	179
Fig 4 SI#8	IQNYIHNEYTIINCM	KNNSGWKISIRGNRI	TWTLIDINGKTKS	FEYNIREDISEYINR	WFFVTITNNLNNAKI	YINGKLESNTDIKDI	180
Ac# M81186	IQNYIHNEYTIINCM	KNNSGWKISIRGNRI	TWTLIDINGKTKS	FEYNIREDISEYINR	WFFVTITNNLNNAKI	YINGKLESNTDIKDI	180

Paragraph 4.3	1	181	195 196	210 211	225 226	240 241	255 256	270
As filed	REVIANGEIIFKLDG	DIDRTQFIWMKYFSI	FNTELSQSNIEERYK	IQSSEYLKDFWGNP	LMYNKEYYMFNAGNK	NSYIKLKKDSPVGEI	269	
Amended	REVIANGEIIFKLDG	DIDRTQFIWMKYFSI	FNTELSQSNIEERYK	IQSSEYLKDFWGNP	LMYNKEYYMFNAGNK	NSYIKLKKDSPVGEI	269	
Fig 4 SI#8	REVIANGEIIFKLDG	DIDRTQFIWMKYFSI	FNTELSQSNIEERYK	IQSSEYLKDFWGNP	LMYNKEYYMFNAGNK	NSYIKLKKDSPVGEI	270	
Ac# M81186	REVIANGEIIFKLDG	DIDRTQFIWMKYFSI	FNTELSQSNIEERYK	IQSSEYLKDFWGNP	LMYNKEYYMFNAGNK	NSYIKLKKDSPVGEI	270	

Paragraph 4.4	1	271	285 286	300 301	315 316	330 331	345 346	360
As filed	LTRSKYNQNSKYINY	RDLYIGEKFIIRRKS	NSQSINDDIVRKEDY	IYLDFFNLNQEQRVY	TYKFKKEEEKLFLA	PISDSDEFYNTIQIK	359	
Amended	LTRSKYNQNSKYINY	RDLYIGEKFIIRRKS	NSQSINDDIVRKEDY	IYLDFFNLNQEWRVY	TYKFKKEEEKLFLA	PISDSDEFYNTIQIK	359	
Fig 4 SI#8	LTRSKYNQNSKYINY	RDLYIGEKFIIRRKS	NSQSINDDIVRKEDY	IYLDFFNLNQEWRVY	TYKFKKEEEKLFLA	PISDSDELYNTIQIK	360	
Ac# M81186	LTRSKYNQNSKYINY	RDLYIGEKFIIRRKS	NSQSINDDIVRKEDY	IYLDFFNLNQEWRVY	TYKFKKEEEKLFLA	PISDSDEFYNTIQIK	360	

Paragraph 4.5	1	361	375 376	390 391	405 406	420 421	435 436	450
As filed	EYDEQPTYSCQLLFK	KDEESTDEIGLIGH	RFYESGIVFEEYKDY	FCISKWYLKEVKRKP	YNLKLGCNWQFIPKD	EGWTE	439	
Amended	EYDEQPTYSCQLLFK	KDEESTDEIGLIGH	RFYESGIVFEEYKDY	FCISKWYLKEVKRKP	YNLKLGCNWQFIPKD	EGWTE	439	
Fig 4 SI#8	EYDEQPTYSCQLLFK	KDEESTDEIGLIGH	RFYESGIVFEEYKDY	FCISKWYLKEVKRKP	YNLKLGCNWQFIPKD	EGWTE	440	
Ac# M81186	EYDEQPTYSCQLLFK	KDEESTDEIGLIGH	RFYESGIVFEEYKDY	FCISKWYLKEVKRKP	YNLKLGCNWQFIPKD	EGWTE	440	

Alignment 5

Exhibit 7 New matter

SEQ ID NO:39 (appearing on page 39 in the specification as filed) has been amended as follows:

Exhibit 7 New matter

At positions 15-17 of paragraph 5.1, TTT is deleted;

- At position 820 of paragraph 5.10, A is inserted;
- At position 933 of paragraph 5.11, T is inserted;
- At position 988 of paragraph 5.11, G is inserted; and
- At position 1226 of paragraph 5.14, A is inserted.

Exhibit 7 New matter

SEQ ID NO:7 (appearing in Figure 4 of the specification as filed) has been amended as follows:

Exhibit 7 New matter

At position 255 of paragraph 5.3, T→C.

Paragraph 5.1

	1	15	16	30	31	45	46	60	61	75	76	90	
Fig 4 as filed	GAATT	CACGAT	GGC	--	CAACAA	ATACA	AT	TCG	AA	CTG	ATG	CTG	87
Fig4 corrected	GAATT	CACGAT	GGC	--	CAACAA	ATACA	AT	TCG	AA	CTG	ATG	CTG	87
P.39 corrected	-----	ATGGC	--	CAACAA	ATACA	AT	TCG	AA	CTG	ATG	CTG	78	
P.39 as filed	-----	ATGGC	TTC	AA	CAACAA	ATACA	AT	TCG	AA	CTG	ATG	CTG	81

Paragraph 5.2

	91	105	106	120	121	135	136	150	151	165	166	180		
Fig 4 as filed	CTG	TCT	GGTT	TACGGT	GCTAAAG	TTGAA	TACGAC	GGT	TTGAA	CAGTT	CAA	CTGACC	TCTCT	177
Fig4 corrected	CTG	TCT	GGTT	TACGGT	GCTAAAG	TTGAA	TACGAC	GGT	TTGAA	CAGTT	CAA	CTGACC	TCTCT	177
P.39 corrected	CTG	TCT	GGTT	TACGGT	GCTAAAG	TTGAA	TACGAC	GGT	TTGAA	CAGTT	CAA	CTGACC	TCTCT	168
P.39 as filed	CTG	TCT	GGTT	TACGGT	GCTAAAG	TTGAA	TACGAC	GGT	TTGAA	CAGTT	CAA	CTGACC	TCTCT	171

Paragraph 5.3

	181	195	196	210	211	225	226	240	241	255	256	270	
Fig 4 as filed	AAGAT	CCG	TGTT	TACT	CAGAA	ATCTCA	ACTCCG	TTC	CTG	AACT	CCG	AAATAC	267
Fig4 corrected	AAGAT	CCG	TGTT	TACT	CAGAA	ATCTCA	ACTCCG	TTC	CTG	AACT	CCG	AAATAC	267
P.39 corrected	AAGAT	CCG	TGTT	TACT	CAGAA	ATCTCA	ACTCCG	TTC	CTG	AACT	CCG	AAATAC	258
P.39 as filed	AAGAT	CCG	TGTT	TACT	CAGAA	ATCTCA	ACTCCG	TTC	CTG	AACT	CCG	AAATAC	261

Paragraph 5.4

	271	285	286	300	301	315	316	330	331	345	346	360	
Fig 4 as filed	AAGA	ACG	ACGG	TATC	CAGAA	TTAC	ATCC	ATCA	CTG	AATA	ACT	CTGGTT	357
Fig4 corrected	AAGA	ACG	ACGG	TATC	CAGAA	TTAC	ATCC	ATCA	CTG	AATA	ACT	CTGGTT	357
P.39 corrected	AAGA	ACG	ACGG	TATC	CAGAA	TTAC	ATCC	ATCA	CTG	AATA	ACT	CTGGTT	348
P.39 as filed	AAGA	ACG	ACGG	TATC	CAGAA	TTAC	ATCC	ATCA	CTG	AATA	ACT	CTGGTT	351

Paragraph 5.5

361	375 376	390 391	405 406	420 421	435 436	450
Fig 4 as filed	GGTAACCGTATCATC	TGGACTCTGATCGAT	ATCAACCGTAAGACC	AAATCTGTATTCTTC	GAATACAACATCCGT	GAAGACATCTCTGAA
Fig4 corrected	GGTAACCGTATCATC	TGGACTCTGATCGAT	ATCAACCGTAAGACC	AAATCTGTATTCTTC	GAATACAACATCCGT	GAAGACATCTCTGAA
P.39 corrected	GGTAACCGTATCATC	TGGACTCTGATCGAT	ATCAACCGTAAGACC	AAATCTGTATTCTTC	GAATACAACATCCGT	GAAGACATCTCTGAA
P.39 as filed	GGTAACCGTATCATC	TGGACTCTGATCGAT	ATCAACCGTAAGACC	AAATCTGTATTCTTC	GAATACAACATCCGT	GAAGACATCTCTGAA

Paragraph 5.6

451	465 466	480 481	495 496	510 511	525 526	540
Fig 4 as filed	TACATCAATCGCTGG	TTCTTCGTTACCATC	ACCAATAACCTGAAC	AATGCTAAATCTAC	ATCAACCGTAAACTG	GAATCTAATACCGAC
Fig4 corrected	TACATCAATCGCTGG	TTCTTCGTTACCATC	ACCAATAACCTGAAC	AATGCTAAATCTAC	ATCAACCGTAAACTG	GAATCTAATACCGAC
P.39 corrected	TACATCAATCGCTGG	TTCTTCGTTACCATC	ACCAATAACCTGAAC	AATGCTAAATCTAC	ATCAACCGTAAACTG	GAATCTAATACCGAC
P.39 as filed	TACATCAATCGCTGG	TTCTTCGTTACCATC	ACCAATAACCTGAAC	AATGCTAAATCTAC	ATCAACCGTAAACTG	GAATCTAATACCGAC

Paragraph 5.7

541	555 556	570 571	585 586	600 601	615 616	630
Fig 4 as filed	ATCAAAGACATCCGT	GAAGTTATCGCTAAC	GCTGAAATCATCTTC	AAACTGGACCGTGAC	ATCGATCGTACCCAG	TTCATCTGGATGAAA
Fig4 corrected	ATCAAAGACATCCGT	GAAGTTATCGCTAAC	GCTGAAATCATCTTC	AAACTGGACCGTGAC	ATCGATCGTACCCAG	TTCATCTGGATGAAA
P.39 corrected	ATCAAAGACATCCGT	GAAGTTATCGCTAAC	GCTGAAATCATCTTC	AAACTGGACCGTGAC	ATCGATCGTACCCAG	TTCATCTGGATGAAA
P.39 as filed	ATCAAAGACATCCGT	GAAGTTATCGCTAAC	GCTGAAATCATCTTC	AAACTGGACCGTGAC	ATCGATCGTACCCAG	TTCATCTGGATGAAA

Paragraph 5.8

631	645 646	660 661	675 676	690 691	705 706	720
Fig 4 as filed	TACTTCTCCATCTTC	AAACCCGAACTGTCT	CAGTCCAATATCGAA	GAACGGTACAAGATC	CAGTCTTACTCCGAA	TACCTGAAAGACTTC
Fig4 corrected	TACTTCTCCATCTTC	AAACCCGAACTGTCT	CAGTCCAATATCGAA	GAACGGTACAAGATC	CAGTCTTACTCCGAA	TACCTGAAAGACTTC
P.39 corrected	TACTTCTCCATCTTC	AAACCCGAACTGTCT	CAGTCCAATATCGAA	GAACGGTACAAGATC	CAGTCTTACTCCGAA	TACCTGAAAGACTTC
P.39 as filed	TACTTCTCCATCTTC	AAACCCGAACTGTCT	CAGTCCAATATCGAA	GAACGGTACAAGATC	CAGTCTTACTCCGAA	TACCTGAAAGACTTC

Paragraph 5.9

721	735 736	750 751	765 766	780 781	795 796	810
Fig 4 as filed	TGGGTAATCCGCTG	ATGTACACAAAGAA	TACTATATGTTCAAT	GCTGGTAAACAAGAAC	TCTTACATCAAACGT	AAGAAAGACTCTCCG
Fig4 corrected	TGGGTAATCCGCTG	ATGTACACAAAGAA	TACTATATGTTCAAT	GCTGGTAAACAAGAAC	TCTTACATCAAACGT	AAGAAAGACTCTCCG
P.39 corrected	TGGGTAATCCGCTG	ATGTACACAAAGAA	TACTATATGTTCAAT	GCTGGTAAACAAGAAC	TCTTACATCAAACGT	AAGAAAGACTCTCCG
P.39 as filed	TGGGTAATCCGCTG	ATGTACACAAAGAA	TACTATATGTTCAAT	GCTGGTAAACAAGAAC	TCTTACATCAAACGT	AAGAAAGACTCTCCG

Paragraph 5.10

811	825 826	840 841	855 856	870 871	885 886	900
Fig 4 as filed	GTGGTGAATCCTG	ACTCGTTCCAATAC	AACCAGAACTCTAA	TACATCAACTACCGC	GACCTGTACATCGGT	GAAAAGTTCATCATC
Fig4 corrected	GTGGTGAATCCTG	ACTCGTTCCAATAC	AACCAGAACTCTAA	TACATCAACTACCGC	GACCTGTACATCGGT	GAAAAGTTCATCATC
P.39 corrected	GTGGTGAATCCTG	ACTCGTTCCAATAC	AACCAGAACTCTAA	TACATCAACTACCGC	GACCTGTACATCGGT	GAAAAGTTCATCATC
P.39 as filed	GTGGTGAATCCTG	ACTCGTTCCAATAC	AACCAGAACTCTAA	TACATCAACTACCGC	GACCTGTACATCGGT	GAAAAGTTCATCATC

Paragraph 5.11

901	915 916	930 931	945 946	960 961	975 976	990
Fig 4 as filed	CGTCGAAATCTAAC	TCTCAGTCCATCAAT	GATGACATCGTACGT	AAAGAAGACTACATC	TACCTGGACTCTTC	AACCTGAATCAGGAA
Fig4 corrected	CGTCGAAATCTAAC	TCTCAGTCCATCAAT	GATGACATCGTACGT	AAAGAAGACTACATC	TACCTGGACTCTTC	AACCTGAATCAGGAA
P.39 corrected	CGTCGAAATCTAAC	TCTCAGTCCATCAAT	GATGACATCGTACGT	AAAGAAGACTACATC	TACCTGGACTCTTC	AACCTGAATCAGGAA
P.39 as filed	CGTCGAAATCTAAC	TCTCAGTCCATCAAT	GA-GACATCGTACGT	AAAGAAGACTACATC	TACCTGGACTCTTC	AACCTGAATCAGGAA

Paragraph 5.12

991	1005 1006	1020 1021	1035 1036	1050 1051	1065 1066	1080
Fig 4 as filed	TGGCGTGTATACACC	TACAAGTACTTCAG	AAAGAAGAAGAAAAG	CTTTTCTGCGTCCG	ATCTCTGATTCCGAC	GAACCTCTACAAACACC
Fig4 corrected	TGGCGTGTATACACC	TACAAGTACTTCAG	AAAGAAGAAGAAAAG	CTTTTCTGCGTCCG	ATCTCTGATTCCGAC	GAACCTCTACAAACACC
P.39 corrected	TGGCGTGTATACACC	TACAAGTACTTCAG	AAAGAAGAAGAAAAG	CTTTTCTGCGTCCG	ATCTCTGATTCCGAC	GAACCTCTACAAACACC
P.39 as filed	TGGCGTGTATACACC	TACAAGTACTTCAG	AAAGAAGAAGAAAAG	CTTTTCTGCGTCCG	ATCTCTGATTCCGAC	GAACCTCTACAAACACC

Paragraph 5.13

1081	1095 1096	1110 1111	1125 1126	1140 1141	1155 1156	1170
Fig 4 as filed	ATCCAGATCAAAGAA	TACGACGAACAGCCG	ACCTACTCTTGCAG	CTGCTGTTCAAGAAA	GATGAAGAATCTACT	GACGAAATCGGTCTG
Fig4 corrected	ATCCAGATCAAAGAA	TACGACGAACAGCCG	ACCTACTCTTGCAG	CTGCTGTTCAAGAAA	GATGAAGAATCTACT	GACGAAATCGGTCTG
P.39 corrected	ATCCAGATCAAAGAA	TACGACGAACAGCCG	ACCTACTCTTGCAG	CTGCTGTTCAAGAAA	GATGAAGAATCTACT	GACGAAATCGGTCTG
P.39 as filed	ATCCAGATCAAAGAA	TACGACGAACAGCCG	ACCTACTCTTGCAG	CTGCTGTTCAAGAAA	GATGAAGAATCTACT	GACGAAATCGGTCTG

Paragraph 5.14

1171	1185 1186	1200 1201	1215 1216	1230 1231	1245 1246	1260
Fig 4 as filed	ATCGGTATCCACCGT	TTCTACGAATCTGGT	ATCGTATTGCAAGAA	TACAAAGACTACTTC	TGCATCTCAAATGG	TACCTGAAGGAAGTT
Fig4 corrected	ATCGGTATCCACCGT	TTCTACGAATCTGGT	ATCGTATTGCAAGAA	TACAAAGACTACTTC	TGCATCTCAAATGG	TACCTGAAGGAAGTT
P.39 corrected	ATCGGTATCCACCGT	TTCTACGAATCTGGT	ATCGTATTGCAAGAA	TACAAAGACTACTTC	TGCATCTCAAATGG	TACCTGAAGGAAGTT
P.39 as filed	ATCGGTATCCACCGT	TTCTACGAATCTGGT	ATCGTATTGCAAGAA	TACAAAGACT-CTTC	TGCATCTCAAATGG	TACCTGAAGGAAGTT

Paragraph 5.15

1261	1275	1276	1290	1291	1305	1306	1320	1321	1335	1336	1350
Fig 4 as filed	AAACGCAAACCGTAC	AACCTGAAACTGGGT	TGCAATTGGCAGTTC	ATCCCGAAAGACGAA	GGTTGGACCGAATAG	TAAGAATTTC-----					1341
Fig4 corrected	AAACGCAAACCGTAC	AACCTGAAACTGGGT	TGCAATTGGCAGTTC	ATCCCGAAAGACGAA	GGTTGGACCGAATAG	TAAGAATTTC-----					1341
P.39 corrected	AAACGCAAACCGTAC	AACCTGAAACTGGGT	TGCAATTGGCAGTTC	ATCCCGAAAGACGAA	GGTTGGACCGAATAG	TAACCTCTAGAGTCG					1338
P.39 as filed	AAACGCAAACCGTAC	AACCTGAAACTGGGT	TGCAATTGGCAGTTC	ATCCCGAAAGACGAA	GGTTGGACCGAATAG	TAACCTCTAGAGTCG					1337

Paragraph 5.16

1351	1365	1366	1380	1381	1395	1396	1410	1411	1425	1426	1440
Fig 4 as filed -----		1341									
Fig4 corrected -----		1341									
P.39 corrected	AGGCCTGCAG	1348									
P.39 as filed	AGGCCTGCAG	1347									

ALIGNMENTS IN RESPONSE TO REJECTIONS UNDER 35 U.S.C. §102

Alignment 6

Smith SEQ ID NO:7 (hereinafter "Smith7_186) was aligned with the nucleotide sequence of Campbell Eklund 2B (as shown in Figure 2, Campbell page 2258; hereinafter "Cbl_Ek2B"). The primer sequence shown on Campbell page 2256 (Table 2) is depicted here in red letters. Nucleotides 873-1084 of Cbl_Ek2B, to which the Examiner has referred, are depicted here in blue. Identical nucleotides are marked by an asterix highlighted in yellow.

Alignment 7

Smith SEQ ID NO:8 (hereinafter "Smith8_186) was aligned with the amino acid sequence of Campbell Eklund 2B (as shown in Figure 2, Campbell page 2258; hereinafter "Cbl_Ek2B"). Identical amino acids are marked by an asterix highlighted in yellow.

Smith8_186	MANKNSEILNNIILNLRYKDNNLIDLGYGAKVEVYDGVELNDKNQPKLTSSANSKIRVTQNQNIIFNSVPLDFSVSFWIRIPKYKNDGIQNYIHNEYTIINC MKNNSGWKISIRGNRI 120
Cbl_Ek2B	-----TAKGNPESAFEIAGSSILLEFIPPELLIPVVGVLLESYIDNKNKIIKTIDNALTKRVEKWIDMYGLIVAQWLS---TVNTQFYTIKEGMYKALNYQAQALEEII 101
Smith8_186	IWTLIDINGKTKSVFFEYNIREDISEYINRWFVTTNNLNNAKIYINGKLESNTDIKDIREVIANGEIIFKLDGIDRTQPIWMKYFSIFNTELSQSNIIEERYKIQSYSEYLKDFWGNP 240
Cbl_Ek2B	KYKYNIYSEEKS---NININFND-INSKLNDGINQAMDNINDFIN---ECSVSYLMKKMIPALVKKLDFDNTLKKNLLNYIDENKLY---LIGSVEDEKSVDKYLKTIIPPDLS- 208
Smith8_186	LMYNKEYYMFNAGNKNSYIKLKKDSPVGEILTRSKYNQNSKYINYRDLYIGEKPIIRRKSNSQSINDDIVRKEDYIYLDFFNLNQEWRVYTYKYFKKEEEKLFLAPISDSDELYNTIQIK 360
Cbl_Ek2B	-TYTNNEILIKIFNKYNSEILN-NIILNLRYRDNNLIDLGYGAKVEVYDGVKLNDKNQFKLTSSADSKIRVTQNQNIIFNSMFLDFSVSFWIRIPKYRNDDIQNYIHNEYTIINC MKNN 326
Smith8_186	EYDEQPTYSQOLLPKDDEESTDEIGLIGIHRFYESGIVFEEYKDYFCISKWYLKEVKRKPYNLKLGCNWQFIPKDEGWTE 440
Cbl_Ek2B	SGWKISIRGNRIIWT-----LIDINGKTKS--VFPEYN-----IRED----- 361

Alignment 8

Smith SEQ ID NO:7 (hereinafter "Smith7_186) was aligned with the nucleotide sequence of Campbell NCTC 7273 (as shown in Figure 2, Campbell page 2258; hereinafter "Cbl_NCTC"). The primer sequence shown on Campbell page 2256 (Table 2) is depicted here in red letters. Nucleotides 873-1084 of Cbl_Ek2B, to which the Examiner referred, are depicted here in blue. Identical nucleotides are marked by an asterix highlighted in yellow.

Smith7_186 Cbl_NCTC	GAATTCACGATGGCAACAAATACAATTCCGAAATCCTGAACAAATCATCCTGAACCTCGGTTACAAAGACAACTCTGATCGATCTGCTGGTTACGGTGCTAAAGTTGAAGTATAC 120
Smith7_186 Cbl_NCTC	GACGGTGTGAACGTGAAAGAACCGAGTCAAAACTGACCTCTTCCGCTAACTCTAAGATCCGTTACTCGAATCAGAACATCATCTTCAACTCCGTTCCGGACTCTCTGTT 240 -----AACAGCTAAAGGAAATTGGA--AAATGCTTTGAGATTCGAGGAGCCAGTATTCCT-----ACTAGAAATTATACCCAGAACTTTTAATACCTGTAGTTGGAGCT 98
Smith7_186 Cbl_NCTC	TCCCTTCGGATCCGTATCCGAAATACAAGAACGACGGTATCCAGAATTACATCCAAATGAATACACCATCATCAACTGCA/TGAAGAATAACTCTGGTTGGAGATCTCCATCCGGGT 360 TTTTATTAGAAATCATATATTG---ACAATAAAAAATAAATT---ATTAACAAATAGATAATCTTAAAC-TAAAAGAAATGAAAAAT-----GGAGTGTATGTACCGGATT 198
Smith7_186 Cbl_NCTC	AACCGTATCATCTGGACTCTGATCGATATCAACCGTAAAGACCAAATCTGATTTCTCGAATACACATCCGTAAGACATCTCTGAATACATCAATCGCTGGTTCTCTGGATTACATCACC 480 AATAGTAGGCAATGGCTCAACAGT-----TAATACCTAAATTATACAAATAAGGGAAATGTATAAGG---CTTAAAT-TATCAAGCCAAAGCA-TTGGAAAGAAATAATA 304
Smith7_186 Cbl_NCTC	AATAACCTGAAACATGCTAAAATCTACATCAACGGTAAACTTGAATCTAACCGACATCAAAGACATCCGTGAAGTTATCGCTAACCGGTAAATCATCTCAAACCTGGACGGTGACATC 600 AAATACAGATATAATA-TATATTCTGAA--AAAGAAAAGTCAAATATTAAACATGATTAAATGATAATA---AATTCTAAACTTAATGAGGGTTAAAC--CAAGCTATA-GATAATAATA 415
Smith7_186 Cbl_NCTC	GATCGTACCCAGTTCATCTGGATGAAATACCTTCCATCTTCAAC-ACCGAACATGCTCTCAGTCAGTCAGAACCGTACAAGA-TCCAGTCCTACTCCGAATACCTGAAAGACTCT 718 AATAATT-----TATAATGGATG---TTCTGTATCATTTAAATGAAAAAAATGTATCCATTACCTCTAGAAAAT--TACTAGACTTGTATAACTCTCAA-----AAAAAATTGT 521
Smith7_186 Cbl_NCTC	GGGGTAATCCGTGATGTAACAAAGAAATACTATA/TGTCATGCTGGTAACAAAGAACTCTTACATCAAACGAAAGACTCTCCGTTGGTAAATCCCTGACTCTTCCAAATACA 838 TAAATATATA---GATGAA-AATAAAATTATAATTGTGATGGAAAGTCGAGAATATGAAAATCA---AAAGTAAATAAAACTGTAAACCATATGCCGTTGATCTTCAATATA 632
Smith7_186 Cbl_NCTC	ACCGAACACTTAAATACATCAACTACCCGACCTGTACATCGGTAAAAGTCATCAATCCGTAACCGTAACTCTCAGTCCATCAATGATGACATGTAACCTAAAGAAGACTACATCT 958 CCAATGATACAATACTAATAGAAATGTTAATAAAATATAATGCGAAATTAAATAATATT-----ATCTTAAATTAAAGATAT-AAGGATAATA---ATTAA-----TAGATTT 735
Smith7_186 Cbl_NCTC	ACCTGGACTCTTCAACCTGAAATCAGGAATGGCGTGTATACACCTACAAAGTACTTCAGAAAGAAGAAAAGCTTCTGGCTCCG---ATCTCTGATTCGGACGAACCTACAACA 1075 ATCAGGATATG-----GGGCAAAAGGTAGAGGTATATG-AAGGAGTCGAGCTTAAATGATAAAAATCAATTAAACTAGTTCAAGAAATAGTAAGATTAGAGTGAACCAAATCA 846
Smith7_186 Cbl_NCTC	CCAT-CGAGATCAAAGAATACGACGAACCGGACCTACTCTGCCAGCTGCTGTCAGAAGAAGATGAAAGACTCTAGCAGAAATCGCTGTGATCGGTATCCACCGTTCTACGAATCT 1194 GAATATCATATTAAATACTGTGTT-----CCMTGATTAGGGTTAGCTTGGGATAAGAATACCTAA--ATATAAGAATGATGGTATACAAAATTATATTCATAATGAAATATACAATA 958
Smith7_186 Cbl_NCTC	GGTATCGTATTCGAAGAATACAAAGACTACTCTGATCTCCAAATGGTACCTGAGGAAGTTAACGCAACCGTACAACCTGAAA---CTGGGTGCAATTGGAGTTCATCCGAAAG 1312 ATTAAT-TGTAATGAAAAAAATATTGGGCTGGAAAATATCTATTAGGGTAATAGGGATAATAATGGACTTTAATGATAAAATGGAAAACCAAATCGGTATTTTGAAATAACATAAG 1077
Smith7_186 Cbl_NCTC	ACGAAGGTTGGACCGAATAGTAAGAATTC 1341 A-GAAGAT----- 1084

Alignment 9

Smith SEQ ID NO:8 (hereinafter "Smith8_186) was aligned with the amino acid sequence of Campbell NCTC 7273 (as shown in Figure 2, Campbell page 2258; hereinafter "Cbl_NCTC"). Identical amino acids are marked by an asterix highlighted in yellow.

Smith8_186	MANKYNSEILNNIILNLRYKDNNLIDLSGYGAKVEVYDGVELNDKNQFKLTSSANSKIRVTQNQNIIFNSVFLDPSVFWIRIPKYKNDGIQNYIHNEYTIINCMKNNSGWKISIRGNRI 120
Cbl_NCTC	-----TARGNFENAFETAGASILLEFIPPELLIPVVGAFLESYIDNKNKIIKTIDNALTKRNEKWSDMYGLIVAQWLS---TVNTQFVYTIKEGMYKALNYQAQALEEII 101
Smith8_186	IWPLLIDINGKTKSVPPEYNIREDISEYINRWFFVTITNNLNNAKIYINGKLESNTDIKDIREVIANGEIIIFKLDGIDRTQFIWM---KYFSIFNTELSQSNIEERYKIQSYSEYLKDFW 237
Cbl_NCTC	KYRYNIYSEKEKS---NINIDPND-INSKLNEGINQADNINNPINGCSVSYLMKKMIPLAVERK---LLDFDNTLKKNNLNYIDENKLYLIGSABYEKSVNK--YLKTIMPFDLSIY 210
Smith8_186	GNPLMYNKEYYMFNAGNKNSYIKLKKDSPVGEILTRSKYNQNSKYINYRDLYIGEKFIIIRRKSNSQSINDDIVRKEDYIYLDFFNLNQEWRYTYKYPKKEEEKLPLAPISDSDELYNTI 357
Cbl_NCTC	TNDTILIEMFNKYNSEILN-NITLNLRYKDNNLIDLSGYGAKVEVYDGVELNDKNQFKLTSSANSKIR---VTQNQNIIFNSVP---LDPSSVFWIRIPKYKNDGIQNYIHNEYTIINCM 323
Smith8_186	QIKEYDEQPTYSQQLFFKKDEESTDEIGLIGIHRFYESGIVFEEYKDYFCISKWYLKEVKRKPYNLKLGCNWQFIPKDEGWTE 440
Cbl_NCTC	KNNSGWKISIRGNRIIWT-----LIDINGKTKS--VFPEYN-----IRED---- 361

Alignment 10

Smith SEQ ID NO:8 (hereinafter "Smith8_186) was aligned with the amino acid sequence of Halpern (as shown at p. 11189, col. 1, paragraph 4, line 2; hereinafter "Halpern"). Identical amino acids are marked by an asterix highlighted in yellow.

Smith8_186 Halpern	MANKYNSEILNNTITLNRLYKDNNLIDLGYGAKVEVYDGVELNDKNQFKLTSSANSKIRVTQNQNIIFNSVFLDFSVSFWIRIPKYKNDGIQNYIHNEYTIINCMKNNSGWKISIRGNRI 120
Smith8_186 Halpern	IWTLIDINGKTKSVFFEYNIREDISEYINRWFPTITNNLNNAKIYINGKLESNTDIKDIREVIANGEIIIFKLDGDIIDRTQFIWMKYPSIFNTELSQSNIIEERYKIQSYSEYLKDFWGNP 240
Smith8_186 Halpern	LMYNKEYYMFNAGNKNSYIKLKKDSPVGEILTRSKYNQNSKYINYRDLYIGEKPIIRRKSNSQSINDDIVRKEDIYIYLDFFNLNQEWRYTYKYPKKEEEKLPLAPISDSDELYNTIQIK 360
Smith8_186 Halpern	BYDEQPTYSCQLLFKDEESTDEIGLIGIHRFYESGIVFEEYKDYFCISKWYLKEVKRKPYNLKLGCNWQFIPKDEGWTE 440
	-----C-----DKI-----LGCDWYFVPTDEGWT- 19

Alignment 11

Smith SEQ ID NO:7 (hereinafter "Smith7_186) was aligned with the nucleotide sequence of Whalen (Accession M81186; hereinafter "M81186"). A preliminary alignment (not shown) with the full-length nucleotide sequence of Whalen M81186 revealed very little identity over approximately the first 2580 nucleotides. Therefore, this alignment is limited to only nucleotides 2581-4041. Selection of this region was haphazard with consideration given merely to providing some overlap on either end of the region of highest similarity. Identical nucleotides are marked by an asterix highlighted in yellow.

Alignment 12

Smith SEQ ID NO:8 (hereinafter "Smith8_186) was aligned with the amino acid sequence of Whalen (Accession M81186; hereinafter "M81186"). A preliminary alignment (not shown) with the full-length nucleotide sequence of Whalen M81186 revealed very little identity over approximately the first 840 amino acids. Therefore, this alignment is limited to only amino acids 841-1291. Selection of this region was haphazard with consideration given merely to providing some overlap on either end of the region of highest similarity. Identical amino acids are marked by an asterix highlighted in yellow.

Smith8_186	-----MANKYNSIEILNNIILNLRYKDNNLIDLSGYGAKVEVYDGVELNDKNQPKLTSSANSKIRVTQNQNIIFNSVFLDFSVSPWIRIPKYKNDGIQNYIHNEYTIINCMKNNS	109
M81186	SIYTNTDILIEMFNKYNSEIENNIIILNLRYKDNNLIDLSGYGAKVEVYDGVELNDKNQPKLTSSANSKIRVTQNQNIIFNSVFLDFSVSPWIRIPKYKNDGIQNYIHNEYTIINCMKNNS	960

Smith8_186	GWKISIRGNRIIWTLIDINGTKSVFFPEYNIREDISEYINRWPFTITNNLNNAKIFYINGLESNTDIKDIREVIANGEIFFKLDGDIIDRTQFIWMKYFSIFNTELSQSNIIEERYKIQSY	229
M81186	GWKISIRGNRIIWTLIDINGTKSVFFPEYNIREDISEYINRWPFTITNNLNNAKIFYINGKLESNTDIKDIREVIANGEIFFKLDGDIIDRTQFIWMKYFSIFNTELSQSNIIEERYKIQSY	1080

Smith8_186	SEYLKDWFGNPLMYNKEYYMFNAGNKNSYIKLKKDSPVGIELTRSKYNQNSKYINYRDLYIGEKFIIIRRKSNSQSINDDIVRKEDYIYLDFFNLNQEWRVYTYKYFKKEEEKLFLAPISD	349
M81186	SEYLKDWFGNPLMYNKEYYMFNAGNKNSYIKLKKDSPVGIELTRSKYNQNSKYINYRDLYIGEKFIIIRRKSNSQSINDDIVRKEDYIYLDFFNLNQEWRVYTYKYFKKEEEKLFLAPISD	1200

Smith8_186	SDELYNTIQIKEYDEQPTYSQOLLFKKDEESTDEIGLIGIHRFYESGIVFEEYKDYFC1SKWYIKEVRKRKPYNLKLGCNNQFIPKDEGWTE	440
M81186	SDEFYNTIQIKEYDEQPTYSQOLLFKKDEESTDEIGLIGIHRFYESGIVFEEYKDYFC1SKWYIKEVRKRKPYNLKLGCNNQFIPKDEGWTE	1291

Alignment 13

Smith SEQ ID NO:7 (hereinafter "Smith7_186) was aligned with the nucleotide sequence of Jung (as shown at Jung, page 71, Figure 4A; hereinafter "Jung_N-ter"). Identical nucleotides are marked by an asterix highlighted in yellow.

Smith7_186	GAATTCACGATGGCAACAAATACAATTCCGAAATCCTGAACAATATCATCCGTAAACCTCGCITACAAAGACAACAATCTGATCGATCTGTC	120
Jung_N-ter	-----	
Smith7_186	GACGGTGTGAACTGAAAGAACCGAGTTCAAACTGACCTCTCCGCTAACTCTAAGATCCGTGTTACTCAGAAATCAGAACATCATCTTC	240
Jung_N-ter	-----	
Smith7_186	TCCPTCTGGATCCGTATCCGAAATACAAGAACGACGGTATCCAGAATTACATCCACAATGAATACACCATCATCAACTGCATGAAGAA	360
Jung_N-ter	-----	
Smith7_186	AACCGTATCATCTGGACTCTGATCGATAACCGTAAGACCAAATCTGTATTCTCGAATACAACATCCGTGAAGACATCTGAATACA	480
Jung_N-ter	-----	
Smith7_186	AATAACCTGAACAATGCTAAAATCTACATCAACGGTAAACTGGAATCTAATACCGACATCAAAGACATCCGTGAAGITATCGCTAACCGTGAAGAATCATCTC	600
Jung_N-ter	-----	
Smith7_186	GATCGTACCCAGTTCATCTGGATGAAATACTTCTCCA----TCTTCACACCGAACTGTCTCAGTCCAATATC--GAAGAACGGTACAAGATCCAGTCTACTCCGAAATACCTGAAAGAC	714
Jung_N-ter	GATT----GTTCTTTATAGCTGATAAAAAATAGTTTTCCAGATTATCTAAAAACCGAAAGAATAGAAATATAATACAGAGTAATTATAGAAAATGACTTCCCTATAAAT----GAATTAA	151
Smith7_186	TTCTGGGTAATCCGCTGATGTAACAAAAGAATACTATATGTTCAATGCTGTAACAAGAACCTTACATCAAACCTGAAGAAAGACTCTCCGGTTGGTAAATCTGACTCGTTCCAAA	834
Jung_N-ter	TTTTAGA-----TACTGATTAAATAGTAAAATAGAAT----TACCAACTGAAAAATA-CAGAAATCACTTAC--TGATTAAATGAGATTTCCAGTATATAGAAAAC-AACCCCTATAAA	260
Smith7_186	TACAACCGAAACTC-TAAATACATCAACTACCGCGACCTGTACATCGGTAAAAGTTCATCATTCCGTGCAAATCTAACATCTCAGTCCATCAATGATGACATCGTACGTAAAGAACACTA	953
Jung_N-ter	AAAAATTTCACAGATGAAAATACCATCTTCAATATTTATACTC--TCAGACATT	
Smith7_186	CATCTACCTGGACTTCTCAACCTGAAATCAGGAATGGCGTGTATACACCTACAAAGTACCTCAAGAAGAAGAAGAAAAGCTTTCTGGCTCCGATCTCTGATTCGACGAACCTACAA	1073
Jung_N-ter	-----	
Smith7_186	CACCATCCAGATCAAAGAACGACGAAACAGCCGACCTACTCTGGCCAGCTGCTGTTCAAGAAAAGATGAAGAACCTACTGACGAAATCGGTCTGATCGGTATCCACCGTTCTACGAATC	1193
Jung_N-ter	-----	
Smith7_186	TGGTATCGTATTGAAAGAACATCAAAGACTACTTCTGCATCTCAAATGGTACCTGAAGGAAGTTAACCGCAACCGTACACCTGAAACCTGGGTTGCAATTGGCAGTTCATCCGAAAGA	1313
Jung_N-ter	-----	
Smith7_186	CGAAGCTTGGACCGAATAGTAAGAACATTTC	1341
Jung_N-ter	-----	

Alignment 14

Smith SEQ ID NO:8 (hereinafter "Smith8_186) was aligned with the amino acid sequence of Jung (as shown at Jung, page 71, Figure 4A; hereinafter "Jung_N-ter"). The sequence shown in Jung Figure 4B is identical to Jung Figure 4A except residues shown in blue are omitted from Jung Figure 4B. Identical amino acids are marked by an asterix highlighted in yellow.

Smith8_186 Jung_N-ter	MANKYNSEILNNIILNLRYKDNNLIDLGYGAKVEVYDGVELNDKNQPKLTSSANSKIRVTQNQNIIFNSVFLDFSVSFWIRIPKYKNDGIQNYIHNEYTIINCMKNNSGWKISIRGNRI 120 -----KAPGICIDVDNEDLFFIADKNPSN-----LSKNERIEYN-----NQSNYIENDFPPINELILDID----- 55
Smith8_186 Jung_N-ter	IWTLIDINGKTKSVFFEYNIREDISEYINRWFFVTITNNLNNAKIYINGKLESNTDIKDIREVIANGEIIIPKLDGIDRTQFIIWMKYFSIFNTELSQSNIIEERYKIQSYSEYLKDFWGNP 240 LISKIELPSENTESLTDPNVDVPVYEQ-----PAIKKIFTDENTIF-----QYLYSQTF----- 105
Smith8_186 Jung_N-ter	LMYNKEYYMPNAGNKNSYIKLKKDSPVGEILTRSKYNQNQSKINYRDLYIGEKFIIIRRKSNSQSINDDIVRKEDYIYLDFFNLNQEWRYTYKYFKKEEKLFLAPISDSDELYNTIQIK 360 -----
Smith8_186 Jung_N-ter	EYDEQPTYSCQLLFKKDEESTDEIGLIGIHRPYESGIVFEEYKDYFCISKWYLKEVKRKPYNLKLGCNWQPIPKDEGWTE 440 -----

Alignment 15

Smith SEQ ID NO:7 (hereinafter "Smith7_186) was aligned with the nucleotide sequence of SEQ ID NO:22 of Williams (hereinafter "Will22_665"). Identical nucleotides are marked by an asterix highlighted in yellow.

Smith7_186	-----GAATTCAAGATGGCCAACAAATACAATTTCGAAATCCTGAACAATTCATCCTGAACCTGCGTTACAAAGACAACAACTGTGATCGATCTGCTGGTTACGGTGTAAAGTT	111
Will22_665	ATGGCTCGCTGCGTGTACCTTCACTGAATACTCAAGAACATCATCAAACTCCATCCTGAACCTGCGCTACGAATCCAATCACCTGATCGACCTGTCTCGTACGGCTTCCAAAATC	120
Smith7_186	GAAGT--ATACGACGGTG----TTGAACGTACAAGAACCGAGTTCAAACGTGACCTCTTCCGCTAACCTCTAAAGATCCGTGTTACTCAGAACTCAGAACATCATCTTCAACTCCGTATTG	225
Will22_665	AACATCGGTTCTAAAGTTAACCTTCGATCCGATCGAAGAACATCAGATCCAGCTGTTCAATCTGGAATCTGCCAAAATCAGAAGTTATCCGTGAGAAATGCTATCGTATACAACCTATCTAC	240
Smith7_186	CTGGACTTCTCTGTTCTCTGGATCCGATTCGGAAATACAAAGAACGACGGTATCCAGAAATTACATCCACAAATGAATACACCATCATCAACTCGATGAAGAATAACTCTGGTTGAG	345
Will22_665	GAAAATCTCTCACCTCTCTGGATCCGATTCGGAAATACCTCAACTCCATCTCTGAA-----CAATGAATACACCATCATCAACTCGATGGAAAACAATTCTGGTTGAGAA	351
Smith7_186	ATCTCCATCCGGTAACCGTATCATCTGGACTCTGATCGATACTCAACGGTAAGACCAAATCTGTATTCGAAATACACACATCCGTGAA--GACATCTCTGAAATACATCAATCCGTGTT	464
Will22_665	GTATCTCTGAACTACCGGTGAAATCATCTGGACTCTGCAAGGACATCAGGGAAATCAACACGGGTGTTGATATCAAAATCT--CTCAGATGATCACACATCTGACTACATCAATCCGTGAT	470
Smith7_186	CTTCGTTACCATACCAAAATCAAC---TGAACAACTGCTAAAATCTACATCACCGTAAACGGTAAACTG--AATCTAAATCCGACATCAAAGACATCCGTGAAAGTTATCGTAACGGTAAATCATC	579
Will22_665	CTTCGTTACCATACCAAAATCTGCTGAAATACCTCAACACGGGTGCTGATCGACCGAAACCGATCTCCA--ATCTGGTAAACATCCACGGTCTCTAAATACATC	588
Smith7_186	TTCAAACTGGACGGTGACATCGATCGTACCCGAGTTCACTGGATGAAAATACTCTCCATCTCAACACCGAAGTGTCTCAGTCCAATATCGAAGAACGGTACAAGATCCAGTCTTACTCC	699
Will22_665	TTCAAACTGGACGGTTCTCCGTGACACTACCGCTACATCTGGATCAAATACTCTGTTGACAAGAAACTGAAACGAAAAGAAAATCAACAGGCTGTACGGACAACCCACTCCAAATCTC	708
Smith7_186	GAATACCTGAAAGACTCTGGGTAATCCGCTGATGTACAACAAAGAATACTATATGTTCAATCTGGTAACAGAACACTTCTACATCAAACGTTGAAAGAACAGACTCTCCGGTTGGTGAAT-	818
Will22_665	GTTATCTCTGAAAGACTCTGGGTTGACTACCTCGACTACATGCTGAAATCTGATCGACCTCGAACAAACCGTACTCATCTGTTGAGCTCAACAAATCGTTGACGCTCAACATGTAGGTATCCGGGTTACATG	828
Smith7_186	--CCTGACTCTTCCAA--ATACAACCCAGAACACTAAATACAT--CAACTACCGCAGCTGTACATCCGTGAAAAGTTCATCATCCGTGCAAATCTAACTCTCAGTCCATCAATGATGAC	933
Will22_665	TACCTGAAAGTCCCGCTGGTTCTGTTATGACTACCAACATCTACCTGAACTCTTCCCTGTACCGTGGTACCAAAATTCATCATCAAG---AAATACGGCTCTGG--TAACAAGGACAAT	942
Smith7_186	ATCGTACCTAAAGAACGACTACATCTACCTGAGCTCTTCAACCTGAATCAGGAATGGCGTGTATACACCTACAAAGTACTTCA--AGAAAGAGAAAGAAAAGCTTTCCCTGGCTCCG--AT	1049
Will22_665	ATCGTACCCACAACTGATCGTGTACATGTTGAGTAAAGAACAAAGAAATCCGGT---GGCTACCAATGCTCTCAGGGTGGTGTAGAAAAGATCTGCTCTGAAAT	1058
Smith7_186	CTCTGATTCGACGAACTCTACAAACACCATCAGATCAAAAGAACGACGACGACACCCGACCTACTCTGGCAGCTGCTGTTCAAGAAAGATGAAAGAATC--TACTGACGAAATCCGTCTGA	1168
Will22_665	CCCGGACGGTGTAACTGTCAGGTAGTTGAAAT---CCAAGAACGACCGGGTATCATAACAAATGCAAAATGTAACCGAACAAATGGTAACGGTATACGGTTTCA	1174
Smith7_186	TCGGTATCCACCGTTCTACCAATCTGGTATCTTCAAGAAATACAAAGACTACTCTGCAATCTCCAAATGGTACCTGAAAGGAAGTTAACGCAAACCGTACAACCTGAAACTGGGTT	1288
Will22_665	TCGGTTTCCACCGTTCAACAA---TATCGC-----TAAACTGGTTGCTTC--CAACTGGTACAATCGTCAAGATCGAACGTTCTCGACTCTG---GGTT	1264
Smith7_186	CCAATTGGCAGTTCACTCCGAAAGACGAAGCTGGACCGAATA---GTAAGAATTC-----	
Will22_665	GCTCTGGGAGTTCACTCCGGTGTAGTACGGTTGGGTGAACGTCGGTGTAAACCCGGAAAGCTT	1330

Alignment 16

Smith SEQ ID NO:8 (hereinafter "Smith8_186) was aligned with the amino acid sequence of SEQ ID NO:23 of Williams (hereinafter "Will23_665"). Identical amino acids are marked by an asterix highlighted in yellow.

Smith8_186	MA-----NKYNSEILNNIILNLRYKDNNNLDLSGYGAKVEVYDGVELN--DKNQPKLTSSANSKIRVTQNQNIIFNSVFLDFSVSPWIRIPKYKNDGIQNYIHNEYTIINCMKNNSGWK	112
Will23_665	MARLLSTFTEYIKNINTSILNLRYESNHLIDLRSYASKINIGSKVNFPDPIDKQNQIQLFNLESSKIEVILKNAIVYNSMYENFSTSFWIRIPKYFN-SIS--LNNEYTIINCMENNSGWK	117
Smith8_186	ISIRGNRIIWTLIDINGKTKSVFPEYNIREDISYEYINRWPFTIITNN-LNNAKIYINGKLESNTDIKDIREVIANGEIFKLDDGDIIDRQFIWMKYFSIFNTELSQSNIIEERYKIQSYSE	231
Will23_665	VSLNYGEIIWTLQDTQEIJKQRVVFKYSQMINISDYINRWIFVTITNNRLNNNSKIYINGRLIDQKPISNLGNIHASNNIMFKLDGCRDTHRYIWIKYFNLFDKELNEKEIKDLYDNQNSNG	237
Smith8_186	YLKDPWGNPLMYNKEYYMFNAGNKNSYIKLKKDSPVGEILT---RSKYQNNSKYINYRDLYIGEKFIIRRKSNSQSINDDIVRKEDYIYLDFFNLNQEWRYVTTYKYFKKEEEKLPLAPIS	348
Will23_665	ILKDPWGDYLQYDKPYYMLNLYDPNKYVDVNNVGIRGYMLKGPRGSVMTMIYLN-SLYRGTKFIIKKYASGN--KDNIVRNNDRVRVYINVVKNKEYRLATNASQAGVEKILSAEIP	354
Smith8_186	DSDELYNTIQIKEYDEQ-PTYSCQLLFFKDEESTDEIGLIGIHRFYESGIVFEEYKDYFCISKWYLKEVKRKPYNLKGNCNWQFIPKDEGWTE---	440
Will23_665	DVGNLSQLVVMKSKNDQGITNKCKMNLQ--DNNGNDIGFIGPHQFNN-----IAKLVASNNYNRQIERSSR--TLGCSWEFIPVDDGWERPL	438

Alignment 17

Smith SEQ ID NO:7 (hereinafter "Smith7_186) was aligned with the nucleotide sequence of SEQ ID NO:25 of Williams (hereinafter "Will25_665"). Identical nucleotides are marked by an asterix highlighted in yellow.

Alignment 18

Smith SEQ ID NO:8 (hereinafter "Smith8_186) was aligned with the amino acid sequence of SEQ ID NO:26 of Williams (hereinafter "Will26_665"). Identical amino acids are marked by an asterix highlighted in yellow.

Smith8_186	-----MA-----NKYNSEILNNITILNLRYKDNNLIDLSGYGAKVEVYDGVELN--DKNQPKLTSSANSKIRVTQNQNIIPNSVPLDPSVSPWIRIPKYKN	88
Will26_665	MGHHHHHHHHHHSSGHIEGRHMASMARLLSTFTTEYIKNIINTSILNLRYESNHLIDLSRYASKINIGSKVNFDPIDKDNQIQLFNLESSKIEVILKNAIVYNSMYENFSTSFWIRIPKYFN	120
Smith8_186	DGIQNYIHNEYTIINCMKNNSGWKISIRGNRIIWTLLIDINGKTKSVFFPEYNIREDISEYINRWPFVTITNN-LNNAKIYINGKLESNTPIKDIRREVIANGEIIFKLDGDIDRTOPIWMKY	207
Will26_665	-SIS-LNNEYTIINCMENNSGWKVSLNYGEIIWTLQDTQEIKQRVVFKYSQMINISDYINRWIFVTITNNRLNNNSKIYINGRLIDQKPISNLGNIHASNNIMFKLDGCRDTHRYIWIKY	237
Smith8_186	FSIFNTELSQSNIIEERYKIQSYSEYLKDFWGNPLMYNKEYYMFNAGNKNSYIKLKKDSPVGEILT---RSKYNQNSKYINYRDLYIGEKPIIIRRKSNSQSINDDIVRKEDYIYLDFFNLN	324
Will26_665	FNLFDKELNEKEIKDLYDNGQNSGILKDFWGDYLQYDKPYMLNLYDPNKVVDVNNVGIRGYMYLKGPGRGSVMTTNLYLNS-SLYRGTKFIKKYASGN--KDNIVRNNDRVYINVVKLN	354
Smith8_186	QEWRVYTYKYFKKEEEKLFALAPISDSDELYNTIQUIKEYDEQ-PTYSCQLLFKKDEESTDEIGLIGIHRPYESGIVFEELYKDYFCISKWYKLEVKRKPYNLKLCGNWQFIPKDEGWTE--	440
Will26_665	KEYRLATNASQAGVEKILSALEIPDVGNLSQVVVMKSNDQGITNKCKMNLQ--DNNNGNDIGFIGFHQFNN-----IAKLVASNWNYRNQIERSSR--TLGCSWEPIPVDDGWERPL	462

Alignment 19

Smith SEQ ID NO:7 (hereinafter "Smith7_186) was aligned with the nucleotide sequence of SEQ ID NO:27 of Williams (hereinafter "Will27_665"). A preliminary alignment (not shown) with the full-length nucleotide sequence of Will27_665 revealed very little identity over approximately the first 2520 nucleotides. Therefore, this alignment is limited to only nucleotides 2521-3891. Selection of this region was haphazard with consideration given merely to providing some overlap on either end of the region of highest similarity. Identical nucleotides are marked by an asterix highlighted in yellow.

Smith7_186	-----GAATTCACTGGCCAAACAAATACAATTCCGAAATCCCTGAACAATATCACTCTGAAC 57
Will27_665	-----GTTAAATAACACTTACAGATACCTTTCAGCTTCCAATACGTAGATAATCAAAAGATTATTCATCTACATTACTGAATATTAAGAATATTAACTAATCTATATTGAAT 2640
Smith7_186	CTGCGTTACAAGACAACAATCTGATCGATCTGCTGGTTACGGTGCTAAAGTTGAAGT--ATACGACGGT-----TTGAACTGAATGACAAGAACCGATCTCAAACGTGACCTCTCCGCT 171
Will27_665	TTAAGATGAAAGTAATCAATTAGACTTATCTAGGTATGCATCAAAATAAATTGGTAGTAAAGTAAATTGGATCCAATAGATAAAATCAATTAACTCAATTATTAAATTAGAA 2760
Smith7_186	AACCTCTAAAGATCCCTGTTACTCGAAGACATCATCTTCAACTCCGTATTCCTGGACTCTCTCTGGATCCCTATCCCGAAATACAAGAACGACGGTATCCAGAAATTAC 291
Will27_665	AGTAGTAAATTGAGGTAATTCTAAATGCTATTTGTTATATAAGTATGTTAGTAACTAGCTTTGGATAAGAATTCCTAAGTATTAAACAGTATAAGCTAAAT--- 2877
Smith7_186	ATCCACAAATGAATACACCATCATCAACTCGATGAAGAATACTCTGGTTGGAGATCTCCATCCGGCTAACCGTATCATCTGGACTCTGATCGATAACACGGTAAGACCAAACTCTGTA 411
Will27_665	-----AATGAATATACAATAAAATGTTGAAAATTAATCAGGATGAAAATCTACCTTAATTGTTGAAATACTCGAACCTTACAGGATACTCAGGAAATAAAACAAAGAGTA 2991
Smith7_186	TTCTTCGAATACACATCCGTGAAGACATCTGAAATACATCAATCGCTGGTTCTCGTTACCTACCAATAAC---CTGAAACATGCTAAATCTACATCAACGGTAACCTGG--AAT 526
Will27_665	GTTTTTAAATACACTCAATGATTAATATCAGATAATAAACAGATGGATTTGTTAATCTACTAAATAAGATAAAATAACTCTAAATTTATATAATGGAAAGTTAATAGAT 3111
Smith7_186	CTAATACCGACATCAAAGACATCCGTGAAGTTATCGTAACCGGAAATCATCTTCAACTGGACGGTGACATCGATCGTACCCAGT--CATCTGGATGAAATACCTCCATCTCAAC 645
Will27_665	CAAAACCAATTCTCAA---ATTAGGTAAATATTCATGCTACTAAATAATGTTAAATTAGATGCTCTAGAGAT--ACACATAGATAATTGGATAAAATATTGTTAATCTTTTGAT 3228
Smith7_186	ACCGAACTGTCAGTCCAAATATCGAAGAACGGTACAAGATCCAGTCTACTCCGAATACCTGAAAGAACCTCTGGGTAATCCGCTGATGTCACAAAGAACATACTATGTTCAATGCT 765
Will27_665	AAGGAATTAAATGAAAAAACAACTAAAGATTATACTGATAATCAATCAAATTCAGGTTATTAAAGACTTTGGGTGATTATTACATATGATAAACCATACTATATGTTAAATTAA 3348
Smith7_186	GGTAACAAGAACACTTACATCAAACGTGAAGAA---AGACTCTCCGGTTGGTAAATCTGACTCGTCCAAATACAACCGAAACTCTAAATACATCAACT---ACCGCAGCTGTACATC 879
Will27_665	TATGATCCAAATAATATGTCGATGTAATAATGTTAGGTTATGTTACCTTAAAGGGCTAGAGGTAGCTTAATGACTCAAACATTATTTAAATTCAAGTTGTTAGTAGG 3468
Smith7_186	GCTGAAAAGTTCACTCATCCGTCCAAATCTCACTCTCACTCAATGACATCTGCTACGGAAAGACTACCTACCTGGGACTCTTCACCTGGGACTCTTCACCTGAAATGCGGTGTTATAC 999
Will27_665	GGGACAAATTTTAAATAA---AAATATGCTTCGG---AATAAAAGATAATATTGTTAGAAATATGATCGTGTATATAATTGTTAGTAAATGAGTTAAAGAATATAGGTTAGCT 3582
Smith7_186	ACCTACAAGTACTTCAAGAAAGAAGAACGGCTTTCTGGCTCGA---TCTCTGATTCCGACGAACTCTACAACACCAATCCAGATCAAAGAATACGACGAAACAGCGGCACCTACTCTT 1117
Will27_665	ACTAAT---GCATCACAGGCCAGGCTAGAAAAAATCTAAGTGCATTAGAAATACCTGATGTTAG---GAAATCTAAGTCA---AGTAGTAGTAATGAAAGTCAAATGATCAAGGAATAACA 3696
Smith7_186	GCCAGCTCTGTTCAAGAAAGATGAGAAATCTACTGACGAAATCGGTCTGATCGGTATCCACCGTTCTACGAATCTGGTATCGTATTGAAAGAACATAAAAGACTACTCTGCACTCTCA 1237
Will27_665	AATAAATCC-----AAATGAA---TTTAC---AAGATAATAATGGGAATGATATAGGC---TTTATAGGTTTC---ATCAGTTAAATATAGCTAAACTAGTAGAGCAACT---A 3792
Smith7_186	AATGGTACCTGAAAGAAGTTAAACGCAACCGTACACCTGAAACTGGGTTGCAATTGGCAGTTCTACCCGAAAGACGAAAGGTTGGACCGAAATGAGTAAGAATTC 1341
Will27_665	ATTGGTATAATAGACAAATAGAAAG-ATCTAGTAGGACTT---TGGGTTGCTCATGGAAATTATTCCTGTAGATGATGGATGGGAGAAAGGCCACTGTAA 3890

Alignment 20

Smith SEQ ID NO:8 (hereinafter "Smith8_186) was aligned with the amino acid sequence of SEQ ID NO:28 of Williams (hereinafter "Will28_665"). A preliminary alignment (not shown) with the full-length amino acid sequence of Will28_665 revealed very little identity over approximately the first 840 amino acids. Therefore, this alignment is limited to only amino acids 2521-3891. Selection of this region was haphazard with consideration given merely to providing some overlap on either end of the region of highest similarity. Identical amino acids are marked by an asterix highlighted in yellow.

Smith8_186	-----MANKYNSEILNNIILNLRYKDNNLIDLSGYGAKVEVYDGVELN--DKNQFKLTSSANSKIRVTQNQNIIFNSVFLDFSVSFWRIPKYKNDGIQNY 94
Ophd28_665	VNNTLSTDIPFQLSKYVDNQRLLSTPTEYIKNIINTSLNLRYESNHLDLRSYASKINIGSKVNPDPIDKNQIQLFNLESSKIEVILKNAIVVNSMYENFSTSFWRIPKYPN-SIS-- 957
Smith8_186	IHNEYTIINCMKNNSGWKISIRGNRIIWTLIDINGTKTSVFFPEYNIREDISEYINRWFVTITNN-LNNAKIYINGKLESNTDIKDIREVIANGEIIFKLDGDDIDRTQPIWMKYFSIFNT 213
Ophd28_665	LNNEYTIINCMENNSGKVSILNYGEIIIWTLQDTQEIKQRVVFKYSQMINISDYINRWIFVTITNNRLNNSKIYINGRLIDQKPISNLGNIIHASNNIMFKLDGCRDTHRYIWIKYFNLFDK 1077
Smith8_186	ELSQSNIEERYKIQSYSEYLKDFTGNPLMNYKEYYMFNAGNKNSYIKLKKDSPVGEILT---RSKYNQNSKYINYRDLYIGEKFIIIRRKNSNQSINDDIVRKEDYIYLDFNQLEWRVY 330
Ophd28_665	ELNEKEIKDLYDNQSNSGILKDFWDGYLYQYDKPYYMLNLYDPNKYVDVNNVGIRGYMYLKGRGSVMTNIYLNS-SLYRGTKFIIKKYASGN--KDNIVRNNDRVYINVVKNKEYRLA 1194
Smith8_186	TYKYPKKEEEKLFPLAISDSDELYNTIQIKEYDEQ-PTYSCQLLPKKDEESTDEIGLIGJHRYFYESGIVFEEYKDYFC1SKWYLKEVKRKPYNLKGNCNWQFIPKDEGWTE--- 440
Ophd28_665	TNASQAGVEKILSALEIPDVGNLSQLVVMKSKNDQGITNKCKMNLQ--DNNGNDIGFIGFHQFNN-----IAKLVASNWYNRQIERSSR--TLCCSWFIPVDDGNGERPL 1296